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A COST AND OUTCOME ANALYSIS OF KIDNEY TRANSPLANTATION: THE IMPLICATIONS OF INITIAL IMMUNOSUPPRESSIVE PROTOCOL AND DIABETES

(FINAL REPORT: VOLUME I)

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DEDICATION

(1) To the patients who, without just reward, gave of themselves for the sole purpose of scientific inquiry.

(2) To the transplant professionals who have made transplantation a clinical reality and a policy enigma.

(3) To those investigators who struggle to understand why life, despite its adversity, remains worth living.

FOREWORD

A report such as this represents the combined efforts and sacrifices of many individuals. In this short foreword, it is impossible to do justice to each and every person who has contributed to the report. I will, nonetheless, attempt to do so.

The sponsor of the study--the Health Care Financing Administration (HCFA)--deserves first and foremost credit since, in the absence of its support, this study would not have been possible. Of the HCFA staffpersons associated with the project, two deserve individual recognition. They are: Dr. Henry Krakauer and Dr. Paul Eggers. Before taking his present assignment at HCFA, Dr. Krakauer was very instrumental in both the conceptualization and the implementation of this study. He worked directly with the American Society of Transplant Surgeons (ASTS) and gained their support for the study. He also assisted in the recruitment of the transplant centers that were eventually chosen to participate in the study.

Dr. Paul Eggers was our Project Officer, and was always available to assist us during the course of the study. His own research on end-stage renal disease (ESRD) is recognized internationally and is very apparent in this report. Dr. Eggers is to be commended for his patience. We were unable to meet the deadline for our final report and Dr. Eggers most graciously extended the due date. Moreover, he thoroughly received the final report and performed additional analyses he thought would add substance to the report. The results of these analyses have been incorporated throughout this report.

As alluded to above, the American Society of Transplant Surgeons endorsed this study from the very outset. Several ASTS members reviewed the study protocol, and transmitted comments and suggestions to Dr. Krakauer. Among these people were the following individuals: Dr. Darrell Campbell, Jr. (University of Michigan), Dr. Robert Gordon (University of

Pittsburgh), Dr. Barry Kahan (University of Texas, Houston), Dr. Fred Sanfilippo (Duke University), Dr. Hans Sollinger (University of Wisconsin), Dr. Everett Spees (Grow Surgical Group and the University of Colorado), Dr. David Sutherland (University of Minnesota), and Dr. Nicholas Tilney (Harvard University). All of these people are to be thanked for their efforts, however small, to insure the success of the study.

As is usually the case, we appointed an advisory committee to the study. The purpose of this committee was to provide overall scientific and technical direction for the study. The following individuals served on the advisory committee: Dr. Christopher R. Blagg (Northwest Kidney Center), Dr. John Crowley (Fred Hutchinson Cancer Research Center), Dr. Ronald Ferguson (Ohio State University), Dr. Alan Hull (independent consultant), and Dr. Oscar Salvatierra (University of California, San Francisco). Dr. David Fryd (University of Minnesota), Dr. Darrell Campbell, and Dr. Everett Spees all attended one or more of the advisory committee meetings. All of these people deserve recognition and thanks for the many contributions they made to the conduct of the study and the preparation of this report. They are not, however, responsible for any of its deficiencies.

As is apparent from this report, the data collection activities associated with this study were immense. Each of the participating transplant centers recruited their own staff for extracting medical records and persuading patients to participate in the study. Without the superb efforts of these individuals, this study would have been an organizational disaster. The people who assured the quality of the data collection effort were as follows: Ms. Paula Cahill (University of California, San Francisco), Ms. Becky Miller and Mr. Richard Wright (Ohio State University), Ms. Annette Brown, Ms. Vicky Floravanti, and Ms. Kathy McCaffrey (all University of Pittsburgh), Ms. Linda

Schoenberg and Ms. Pam Graves (University of Texas, Houston), and Ms. Gladys Simon (University of Wisconsin).

Data collation, coding, and analysis are all time consuming and complicated tasks. For purposes of this study, many people contributed in a wide variety of ways. Among these people are the following: Ms. Cynthia Livak and Ms. Judith Raab (both of whom came to know most of the patients in this study personally), Ms. Lair Showalter, Ms. Donna McLynne, and Mr. Tony Maier. The majority of all data analysis tasks were conducted by Ms. Claudia Thompson. Finally, Mr. William Grady provided expert assistance with the analysis of the survival data.

Preparation of interim reports as well as the final report represents the combined efforts of several individuals. We cannot possibly thank the enormously qualified people who worked on these. Up until the preparation of the final report, Ms. Millie Gregory (retired) served as the project secretary. Six people contributed to the preparation of the final report: Ms. June Hull, Ms. Anita Stocker, Ms. Paula Roberts, Ms. Moira McDonald, Ms. Donna McLynne, and Ms. Janine Jensen. As is apparent, the preparation of this report was a huge task requiring coordination among scientists, research assistants, data collectors, and secretarial personnel. These activities were very ably coordinated by Ms. Hull, Ms. McLynne, and Ms. McDonald.

In addition, I would like to take this opportunity to recognize the many contributions of Dr. Diane L. Manninen to the conduct of this study, and the preparation of this report. Shortly after we received the cooperative agreement from HCFA to conduct the study, I personally became very involved in many activities related to organ transplantation, including the National Task Force on Organ Transplantation. These activities considerably reduced the time I had available to spend on this project. As a result, Dr. Manninen took charge of the entire research endeavor. She supervised all aspects of data collection and data analysis and, ultimately, she independently wrote a large share of the final report. Only during the past six months have I had the time available to assist Dr. Manninen. Therefore, in the final analysis I must acknowledge that Dr. Manninen was the Project Director for this study. Although I provided technical input and project-related advice, Dr. Manninen took the lead during the entire course of this study.

Unfortunately, Dr. Manninen is rarely recognized for her individual efforts, as she often stands in my own "professional shadow." I would, however, be less than honest if I did not point out that Dr. Manninen was the key to the success of this study. In this regard, her personal efforts should overshadow those of mine when a judgment is made as to the lasting contribution of this study. I am forever grateful to Dr. Manninen for her mild manner, her great patience and understanding, and her considerable research skills. In my assessment, there are few people with whom I can work closely day-to-day. Dr. Manninen is foremost among them. As a tribute to our joint efforts, we continue to work together as both mutual and equal collaborators.

Finally, over the past five years many individuals have greatly contributed to my professional success. Some of these people have already been mentioned, but others, too, deserve recognition. Rather than cite their individual contributions, I will simply list their names. I trust that each of the following persons can understand the reasons and the extent of indebtedness that I owe them. They are, in alphabetical order: Remy Arnoff, Nancy Ascher, Larry Bauer, Charles R. Baxter, Christopher R. Blagg, Joel Broida, Peter Bouxsein, Lisa Bowen, Clive O. Callender, Arther Caplan, Jean Carosella, James Childress, Jack G. Copeland, Robert Corry, Nancy Cummings, Donald Denny, Louis Diamond, Ronald Dreffer, Leatrice Ducat, Paul Eggers, John Entine, Ronald Ferguson, Rene Fox, Louis P. Garrison, Jr., Heidi Gerstman, Barbara Gill, Nancy Goeken, Jon Gold, Robert Gordon, Albert R. Gore, Jr., Millie Gregory, Robert Gutman, John Hansen, Mark Hardy, L. Gary Hart, Marilyn Hoe, Alan Hull, June Hull, Larry Hunsicker, Olga Jonasson, Phil Jos, Carl Josephson, Paul Keown, Stuart Kleit, Richard Knox, C. Everett Koop, Henry Krakauer, Nancy Kutner, Jimmy Light, Cynthia Livak, Tony Maier, Jerry Mande, Diane L. Manninen, Tom Marchioro, Franklin McDonald, John McDonald, Steven D. McLaughlin, Donna McLynne, Karen Merriken, Libby Merrill, George K. Mitchell, John Najarian, Howard Nathan, John Newmann, Thomas Overcast, Philip Oyer, Cindy Perry, Gene Pierce, Jeffrey Prottas, John Purvis, Judith Raab, Barbara Rader, Keith Reemtsma, Mark Reiner, Dick Rettig, James Richards, John A. Robertson, Eric Rose, Paul Russell, Fred Sanfilippo, Oscar Salvatierra, Ralph Schaffarzick, Spencer Schron, Jane Schultz, Linda Sheaffer, Roberta Simmons, Hans Sollinger, Thomas Starzl, Calvin Stiller, Terry Strom, David Sutherland, Paul Terasaki, Claudia Thompson, Jane Warmbrodt, and William K. Vaughn.

Last, but not least, I want to recognize my wife (Pam) who has learned to live without a husband, and my daughter (Alison) who has found her way without her father.

Roger W. Evans, Ph.D
Mercer Island, Washington
August, 1989

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Introduction

The results of kidney transplantation improved markedly following the introduction of cyclosporine. The greatest improvement was experienced by patients who received cadaveric grafts, where patient and graft survival have increased from a mean of 87 and 57 percent, respectively, at one year with conventional immunosuppressive therapy (i.e. azathioprine and prednisone), to 95 and 80 percent with some variation of cyclosporine therapy (Bradley et al., 1986:568; Borel, 1983:2219; Calne, 1987:506; Calne and Wood, 1985:549; Evans, 1984:127; Ferguson, et al., 1982; Hakala et al., 1983:465; Merion et al, 1984; Najarian et al., 1983:2463; Najarian et al, 1983:438, Stiller and the Canadian Transplant Study Group, 1983:2479; Starzl et al., 1983:2459). Therefore, it was not surprising that, following Food and Drug Administration (FDA) approval in November of 1983, there was a nearly wholesale shift in the immunosuppressive management of transplant recipients, both in the United States and abroad. However, the success observed was not without severe economic implications. Cyclosporine proved to be an expensive drug, with annual per patient expenditures initially projected to be between $5,000 and $6,000 (Evans, 1984:127). These costs paled in comparison to conventional immunosuppressive therapy which was estimated to cost between $1,000 and $1,500 per patient year. To justify the added costs associated with cyclosporine, it was argued that the drug was more effective than conventional immunosuppression, the additional benefits being worth the added costs (Henry et al., 1985:533). For example, it was consistently argued that transplant recipients receiving cyclosporine had fewer posttransplant complications, a decreased incidence of infection and rejection, and a shorter initial hospital stay.

Evidence supporting the "cost-effectiveness" of cyclosporine therapy was scant, and it was unclear whether the much higher costs of immunosuppression could be justified in the long-term. Perhaps the most useful data supporting the "cost-effectiveness" of cyclosporine therapy was amassed and presented in Congressional testimony by Dr. Ronald Ferguson, then of the Ohio State University, but based on his experience while at the University of Minnesota (Henry et al., 1985:533). Technically, Ferguson did not conduct a formal cost-effectiveness analysis, but, rather, performed a cost analysis, outlining both the costs and the benefits of cyclosporine. He did not directly compare the costs and benefits of cyclosporine therapy with those of conventional immunosuppressive therapy. Nonetheless, the evidence Ferguson presented was intuitively appealing and served to sensitize Congress to the likely financial needs of transplant recipients. It was readily apparent that many patients would be unable to afford cyclosporine therapy, thus placing their newly acquired grafts at grave risk (Task Force on Organ Transplantation, 1985).

Historically, over 90 percent of all kidney transplant recipients in the United States are transplanted under the auspices of the Medicare program. While Medicare covers the costs associated with the patient's surgery, and all inpatient drugs, outpatient prescription drugs have historically been the responsibility of the patient. Because of the high cost of cyclosporine, it came as no surprise that there were numerous members of the transplant community who felt that Medicare benefits should be extended to include payment for outpatient immunosuppressive drugs for kidney transplant recipients. For many reasons, the Health Care Financing Administration (HCFA) was concerned about the implications of paying for outpatient immunosuppressive drugs. Payment for such drugs would certainly be an add-on cost to the Medicare program. Also, it was felt that cyclosporine was not a cost neutral drug, regardless of who paid. In other words, the benefits patients received would not be sufficient to offset the added cost of the drug. These concerns were legitimate.

In a detailed analysis of the costs associated with various immunosuppressive drugs, the National Task Force on Organ Transplantation concluded that cyclosporine was a cost-effective agent, particularly if patients were converted from cyclosporine therapy to conventional immunosuppressive therapy (i.e. azathioprine and prednisone) within one-year posttransplant (Task Force on Organ Transplantation, 1985). However, the routine conversion of cyclosporine patients has not occurred as anticipated, and an increasingly larger fraction of both living-related and cadaveric donor transplant recipients are being placed on cyclosporine. Based on an analysis conducted by Eggers, Table 1-1 indicates the percentage of kidney transplant recipients by year, according to source of graft, who were on cyclosporine. Clearly, cyclosporine is a very widely used drug, the economic implications of which are considerable and must be fully evaluated. This is the objective of this report, although some of the more salient results of our analysis of costs are summarized below.

Per patient immunosuppressive drug costs vary depending upon the patients' weight, the drug dosage required, and various immunological considerations, not all of which are fully understood. Moreover, the therapeutic goal is to gradually taper all immunosuppressive agents to achieve immunological tolerance, but not to increase the patient's susceptibility to

Table 1-1

Percentage of Kidney Transplant Recipients Receiving Cyclosporine by Year According to Source of Graft

	Source of Graft	
Year	Living-Related Donor	Cadaveric Donor
1983	12%	18%
1984	34%	62%
1985	51%	78%
1986	58%	88%
1987	77%	92%

SOURCE: Paul Eggers, HCFA, December 15, 1988.

infection. As we have gained experience with the various drugs in use today, our estimates of dose requirements have changed. Our current experience suggests that cyclosporine dosage requirements were excessively high during the early period of experimentation with the new agent (Myers, 1986:964). Today, with multiple drug protocols, the dosage requirements for cyclosporine have declined significantly, thus having important cost implications. Data relevant to the costs of various maintenance protocols are summarized in Table 1-2 and are described in greater detail in Chapter 13. As shown, there are considerable variations in the costs associated with various immunosuppressive drug protocols according to early and late experience. Moreover, even within a given period, costs differ according to protocol.

Given these results, concerns persist as to the relative cost-effectiveness of cyclosporine therapy in comparison with conventional immunosuppressive therapy. These concerns, of course, were what the present study was intended to address. Unfortunately, because of the widespread adoption of cyclosporine, it is difficult to conduct a true cost-effectiveness analysis. For the most part, patients who are not on cyclosporine have developed clinically adverse reactions which preclude the maintenance use of cyclosporine. In short, patients cannot be readily randomized between conventional and cyclosporine therapy. Nonetheless, this observational study, with its attendant shortcomings, was intended to address a myriad of issues related to immunosuppressive therapies.

In the remainder of this chapter we will attempt to provide an appropriate context for the entire report. We begin with a summary statement of the objectives of the study, and then proceed to highlight some

Table 1-2

Maintenance Immunosuppressive Drug Costs by Protocol During Early and Late Experience

	Protocol Phase		Annual Maintenance Costs	
Protocol	Induction	Maintenance	Early Experience	Late Experience
Conventional	AZA+PRED	AZA+PRED	$ 793	$ 793
Conventional	AZA+PRED+ALG	AZA+PRED	793	793
Double-Drug	CSA+PRED	CSA+PRED	8,198	4,028
Triple-Drug	AZA+PRED+ALG	CSA+PRED	8,227	3,157
Quadruple Drug	AZA+PRED+CSA+ALG	AZA+PRED+CSA	6,870	3,293

NOTES:
AZA = azathioprine
PRED = prednisone
ALG = antilymphocyte globulin
CSA = cyclosporine

of the features of what might be referred to as the ESRD policy dilemma. Next we examine transplantation in the context of the management of ESRD patients and, finally, we conclude with a detailed review of various End-Stage Renal Disease Program statistics, many of which have been taken from HCFA's annual report to Congress.

Study Objectives

This research project was ambitious from the outset. The research proposal was submitted to HCFA just after Food and Drug Administration Approval (FDA) of cyclosporine. It was our hope that patients could be randomized prospectively to conventional immunosuppressive therapy and some variation of cyclosporine therapy. At the time, double-drug therapy was being adopted by many teams throughout the United States. Unfortunately, because the initial clinical experience with cyclosporine was so overwhelmingly positive, it became evident that a randomized study was not feasible. In fact, some would argue that it was ethically inappropriate to randomize patients. Therefore, we were forced to settle with an observational study--a more or less natural history of the evolution of the application of various immunosuppressive drugs at five major transplant centers in the United States. These centers were: (1) the University of California at San Francisco, (2) the Ohio State University, (3) the University of Pittsburgh, (4) the University of Texas at Houston and (5) the University of Wisconsin at Madison.

We were initially disappointed because of the inherent lack of control in an observational study. We felt it would be difficult to arrive at any firm conclusions and that the results of the study would be suspect. However, the value of this observational study became apparent as transplant teams began to experiment with triple-and quadruple-drug therapy. We were in an ideal position to document the costs and outcomes of various approaches to immunosuppressive therapy. As it turns out, two centers continued to use double-drug therapy throughout the course of the study--the University of Pittsburgh and the University of Texas at Houston. The three remaining centers experimented with triple and quadruple induction therapy--the University of California at San Francisco, the Ohio State University, and the University of Wisconsin at Madison. In short, the patients in this study can be divided into two groups, by center, according to the initial immunosuppressive protocol under which they received their transplant.

The objectives of the study were modified to some extent to take into account the altered study design and the protocol changes of the participating transplant centers. The study objectives are as follows:

(1) To examine the characteristics of patients assigned to various immunosuppressive therapies.

(2) To determine the extent to which patients on various immunosuppressive protocols experience different outcomes (e.g., mortality, graft survival, morbidity, and utilization).

(3) To analyze the quality of life, both objective and subjective, of patients on various immunosuppressive therapies.

(4) To analyze both the costs (Medicare reimbursements) and charges (amount billed Medicare) associated with patients on various immunosuppressive therapies, including the cost of initial transplant and the cost of followup care (inpatient hospital costs, physician office visits, outpatient laboratory tests, and prescription drugs).

We were able to meet all our objectives, with the exception of part of the last. Due to time and resource constraints, we were unable to conduct the analysis of Medicare reimbursements. We hope to conduct the required analyses at a later date, pending the availability of complete Medicare reimbursement data on the patients who participated in the study.

The ESRD Health Policy Dilemma

The End-Stage Renal Disease (ESRD) Program of Medicare has been under careful scrutiny since its inception (Bovbjerg et al., 1987:177; Editorial, 1981:55; Evans et al., 1981:487; Moskop, 1987:11; Rettig, 1980). With annual Medicare reimbursements totaling $2.6 billion for just over 100,000 beneficiaries in 1987, the Program is clearly expensive. It has been estimated that about 5.5 percent of Medicare Part B expenditures, and 3.4 percent of total Medicare expenditures are associated with the care of ESRD patients who constitute less than a quarter of one percent of Medicare beneficiaries. As an experiment in national health insurance, some have argued that the Program is a dismal failure, and that resources consumed by ESRD patients would be better spent on preventive health care services and health promotion efforts (Moskop, 1987:11).

Fears associated with the ESRD Program are abundant. The number of ESRD patients continues to increase at a disconcerting rate. For example, between 1986 and 1987 the total number of dialysis patients increased by 8.3 percent (see Table 1-3). Further complicating matters is the adverse case-mix of patients now entering the Program. The greatest growth in the Program is in beneficiaries 75 years of age and older (see Table 1-4). The future of the Program is, thus, uncertain as older, sicker, more debilitated patients become eligible for Medicare benefits (McKevitt et al ., 1986:130; Neu et al., 1986:14). Not surprisingly, the merits of "rationing" health care has become not only a

Table 1-3

Total Number of Patients on Dialysis in the Medicare End-Stage Renal Disease Program

Year	Number of Patients
1968	800
1969	1,000
1970	2,456
1971	3,482
1972	10,000
1973	11,000
1974	18,875
1975	22,000
1976	30,131
1977	32,435
1978	36,463
1979	45,565
1980	53,364
1981	58,770
1982	65,765
1983	71,987
1984	78,483
1985	84,797
1986	90,886
1987	98,432

Table 1-4

Age Distribution of New Enrollees in the Medicare End-Stage Renal Disease Program, 1978, 1982, and 1985

Age (Years)	1978	Year 1982	1985	Average Annual Change 1978-1985 (%)
0-14	333	414	423	3.5
15-24	1,115	1,170	1,183	0.8
25-34	1,758	2,458	2,684	6.2
35-44	2,045	2,595	3,360	7.4
45-54	2,836	3,529	4,191	5.7
55-64	3,443	5,263	6,818	10.3
65-74	2,848	4,574	6,828	13.3
≥75	817	1,812	3,457	22.9
Mean Age (Years)	50.9	53.3	55.5	1.2

SOURCE: Eggers, 1988: 225.

moral debate, but a social issue as well (Evans, 1983:2047; 1983:2208; Daniels, 1986:1380; Reagan, 1988:1149).

Even if the foregoing criticisms are not sufficient to dampen the spirits of those who advocate continued support of the ESRD Program, the critics also point out that the quality of life of ESRD patients is sufficiently compromised to raise questions as to the overall effectiveness of the Program as well. There is evidence, for example, that patients with renal failure frequently choose to forego treatment, thus accepting death as more palatable than the relatively uncertain life of a dialysis patient or that of a transplant recipient (Neu and Kjellstrand, 1986:14; Kjellstrand, 1988:1).

The picture that begins to emerge, at least as painted by the critics, is that the ESRD Program is both costly and ineffective. In an era when cost-effectiveness has become a focal consideration among health care policymakers, it would appear that the ESRD Program is in trouble (Weinstein and Stason, 1977:716; Weinstein et al., 1980; Doubilet et al., 1986:253). The advocates of the Program, including patients and providers, however, have assumed an ever more vigilant posture. They are quick to point out that thousands of lives have been saved at an expense that is no greater than that associated with the care of persons with other catastrophic health conditions. Moreover, the quality of life of the majority of patients is reasonable, given their life circumstances. Many patients are rehabilitated, and many more, it is contended, have considerable potential for rehabilitation.

In short, the advocates of the ESRD Program have an opinion that differs markedly from that of the critics. With adequate financial support, new technological innovations, and programs designed to facilitate patient rehabilitation, ESRD Program advocates are convinced that the future can be brighter than the past--that the ESRD patients of tomorrow will be very different from the ESRD patients of today.

Take, for example, the marked improvements in kidney transplantation that have occurred since 1980 with the early clinical trials of cyclosporine. Graft survival rates have increased dramatically, as noted, and there is evidence that the quality of life of transplant recipients has improved as well (Evans _et al._, 1985:553; Simmons _et al._, 1988:481). Moreover, as a result, more patients are being referred for kidney transplantation, although donor organ availability remains a serious concern. Too few donor kidneys are available to meet the demand for them (see Table 1-5). In a very real sense, transplantation is believed to be the cornerstone as well as the hope of the ESRD Program. Kidney transplantation is, in the minds of many, unarguably the most cost-effective form of treatment for the patient with ESRD. For every patient transplanted, a patient averts dialysis, or is removed from the dialysis patient rolls, at a considerable savings to Medicare, and at great benefit to the patient involved (Eggers, 1988:223). As the supply of donor organs improves, as many contend it will, the ESRD Program will be dominated by transplant recipients as opposed to dialysis patients (see Table 1-6). At present, the ESRD Program is largely a dialysis program, and the advocates for the Program feel that this will change over the next decade.

It is unlikely that dialysis will ever become outmoded therapy for renal failure. Transplant candidate selection criteria, although becoming increasingly liberal, remain quite stringent, considering that the _majority_ of patients in the fastest growing segment of the ESRD patient population--the elderly--do not easily qualify for kidney transplantation (Birtch, 1988:262;

Table 1-5

United Network for Organ Sharing:
Number of Patients Awaiting Kidney Transplants By Month

Month/Year	Number of Patients Awaiting Transplant
December, 1987	11,872
January, 1988	12,009
February, 1988	12,258
March, 1988	12,751
April, 1988	12,891
May, 1988	13,022
June, 1988	13,091
July, 1988	13,251
August, 1988	13,198
September, 1988	13,552
October, 1988	13,703
November, 1988	13,861
December, 1988	13,947
January, 1989	14,071
February, 1989	14,315
March, 1989	14,508
April, 1989	14,777
May, 1989	14,949

Table 1-6

Approximate Number of Cadaveric Kidney Donors by Year

Year	Number of Donors
1980	2,138
1981	2,142
1982	2,300
1983	2,705
1984	3,290
1985	3,637
1986	3,990
1987	4,000
1988	4,083

Terasaki, 1985). However, there are innovations that have also improved the general outlook for dialysis patients. These include, for example, recombinant human erythropoietin (EPO) and high-flux short-term dialysis (Eschbach et al., 1987:73; Erslev, 1987:101; Winnearls et al., 1986:1175). Preliminary evidence clearly indicates that transfusion-dependent dialysis patients no longer require regular transfusions with thrice weekly administrations of EPO. Also, with EPO, anemic patients have a much improved clinical picture, and higher quality of life (Eschbach, et al., submitted). While it is unlikely that EPO will be a cost-neutral innovation, it does have considerable potential for improving the lives of ESRD patients. Unfortunately, the fact that transfusions may no longer be required does not necessarily mean that the direct cost savings will be sufficient to offset the cost of the drug, once Food and Drug Administration approval has been acquired. It is currently estimated that annual per patient expenditures for EPO could be as high as $9,000 (Bankhead, 1988:48). An interesting dilemma is likely to occur; is the Medicare Program willing to pay a higher price for dialysis with adjunctive EPO therapy to improve the overall quality of life of dialysis patients? The answer to this question remains unclear, but is likely to be clarified in the months to come (Paginini, 1988:36; 1988:37).

At this juncture, it is difficult to predict the future of the ESRD Program. There is not an overwhelming mandate to discontinue the program, or to substantially change its essential features. Levels of reimbursement for dialysis services, however, are often targeted for discussion. For example, an attempt was recently made to reduce by $4.00 the composite rate for dialysis. Although unsuccessful, this would not be the first time the composite rate has been reduced. Nonetheless, while there is no evidence that the ESRD

Program is coming upon tumultuous times, there are few signs that positive changes are likely. In short, the Program appears to be somewhat stagnated, although one cannot help but think that this period represents a calm before the storm.

The Clinical and Policy Reality of Kidney Transplantation

In a recent landmark article, Eggers (1988:223) analyzed the effect of transplantation on the Medicare End-Stage Renal Disease Program. He points out that the number of kidney transplant procedures performed from 1980 to 1985 increased by 10 percent each year, and that graft survival rates from cadaver and living related donors increased by seven and three percent, respectively. As a result, he concluded that the fastest growing group of beneficiaries of the Medicare End-Stage Renal Disease Program are those with functioning grafts (i.e., successful transplants). As of the end of 1985, successful kidney transplant recipients accounted for 18 percent of all beneficiaries and 32 percent of all beneficiaries less than 55 years of age. Most noteworthy is the fact that in the youngest age group, transplantation has reached a level sufficient to reduce the absolute numbers of patients on dialysis, beginning in 1983.

Not surprisingly, the economic implications of these changes are significant. As Eggers notes, because the costs of maintaining patients with functioning grafts are only one-third of those for patients on dialysis, and because the quality of life of transplant recipients is generally superior to that of dialysis patients, renal transplantation is causing a convergence of the best clinical and economic outcomes for patients with ESRD.

It is no coincidence that transplantation has had the desirable effect noted here. Improvements in clinical immunosuppression, various legislative initiatives, and changes in the ESRD Program amendments have all encouraged kidney transplantation as an alternative to renal disease. Table 1-7 summarizes various key events in organ transplantation, many of which had implications for renal transplantation.

The events having the greatest significance for kidney transplantation noted in Table 1-7 are as follows:

• June 7-8, 1983	Surgeon General's Workshop
• September 21-22, 1983	Surgeon General's Workshop
• November 14, 1983	Hearings on the Payment of Immunosuppressive Drugs
• October 19, 1984	The National Organ Transplantation Act Becomes Law
• January 23, 1985	Establishment of the National Task Force on Organ Transplantation
• October, 1985	National Organ Transplantation Task Force Report to Congress on Immunosuppressive Therapies Is Issued
• July 14, 1986	Final Report of the National Task Force on Organ Transplantation is Released to the Public
• September 30, 1986	United Network for Organ Sharing Contract is Awarded by the Health and Services Administration
• January 19, 1988	Medicare Program: Medicare Coverage of Immunosuppressive Drugs; Proposed Rule, Federal Register

Table 1-7

Key Events in Organ Transplantation

November, 1979	HCFA Tentatively Authorizes Payments For Heart Transplantations at Stanford University Medical Center
December 7, 1979	NHLBI Submits a Memorandum to the Director of the National Center for Health Care Technology Concerning Medicare Coverage of Heart Transplants
January 21, 1980	NHLBI Submits a Second Memorandum to the NCHCT Concerning Medicare Coverage of Heart Transplants
June 30, 1980	HCFA Issues *Federal Register* Notice "Exclusion of Heart Transplantation Procedures From Medicare Coverage"
January 22, 1981	HCFA Issues *Federal Register* Notice Entitled "Medicare Program; Solicitation of Hospitals and Medical Centers to Participate in a Study of Heart Transplants"
May 13, 1981	HCFA Issues RFP to Conduct a Study Entitled "The Social, Ethical, and Economic Consequences of Medicare Coverage For Heart Transplants"
June 26, 1981	Battelle Submits Proposal to HCFA to Conduct the National Heart Transplantation Study
September 30, 1981	Battelle is Awarded the Contract to Conduct the National Heart Transplantation Study (NHTS)
February, 1983	Met with Dr. Myron Genel (Legislative Aide) to Congressman Albert R. Gore, Jr. to Discuss Transplant Issues

Table 1-7 (continued)

Key Events in Organ Transplantation

April 13-14, 1983	Organ Transplant Hearings (Congressman Gore)
April 27, 1983	Organ Transplant Hearings (Congressman Gore)
June 7-8, 1983	Surgeon General's Workshop on Solid Organ Procurement for Transplantation: Educating the Physician and the Public
June 20-23, 1983	NIH Consensus Development Conference on Liver Transplantation
July 29, 1983	Organ Transplant Hearings (Congressman Waxman)
September 21-22, 1983	Meeting of a Steering Committee for the Formation of a Federation to Encourage Organ Donations for Transplantation (Surgeon General)
September 22, 1983	Formation of the American Council on Transplantation
October 17, 1983	Hearings on Organ Transplants-HR4080 (Congressman Waxman)
October 20, 1983	Hearings on Organ Transplantation (Senator Hatch)
October 31, 1983	Hearings on Organ Transplants-HR4080 (Congressman Waxman)
November 7, 1983	Hearings on Foreign National Transplants (Congressman Gore)
November 14, 1983	Hearings on Payment of Outpatient Immunosuppressive Drugs (Congressman Waxman)

Table 1-7 (continued)

Key Events in Organ Transplantation

January 23-24, 1984	First Meeting of the American Council on Transplantation
February 9, 1984	Hearings on HR-4080 (Congressman Jacobs)
October 19, 1984	The National Organ Transplantation Act (Public Law 98-507) Becomes Law
October, 1984	Final Report for the NHTS is Submitted to HCFA for Review
November, 1984	HCFA Submits NHTS Final Report to the Public Health Service for Review (NCHSR/OHTA)
December 28, 1984	NCHSR/OHTA Sends a Review Memorandum to HCFA Sharply Criticizing the NHTS Report
January 23, 1985	Establishment of the National Task Force on Organ Transplantation
February 11, 1985	First Meeting of the National Task Force on Organ Transplantation
March, 1985	NHTS Project Director Responds to NCHSR/OHTA Memorandum
April 23, 1985	Second Meeting of the National Task Force on Organ Transplantation
May 2, 1985	Secretary of DHHS, Margaret Heckler Holds a Press Conference and Officially Releases the Final Report From the NHTS
June 17-18, 1985	Third Meeting of the National Task Force on Organ Transplantation
August 5-6, 1985	Fourth Meeting of the National Task Force on Organ Transplantation

Table 1-7 (continued)

Key Events in Organ Transplantation

September 30 - October 1, 1985	Fifth Meeting of the National Task Force on Organ Transplantation
October, 1985	National Organ Transplantation Task Force Report to Congress on Immunosuppressive Therapies is Issued
November 18-19, 1985	Sixth Meeting of the National Task Force on Organ Transplantation
December 12, 1985	Labor HHS appropriations bill (99178) for FY 1986 passed
January 9-10, 1986	Seventh Meeting of the National Task Force on Organ Transplantation
March 2-3, 1986	Eighth Meeting of the National Task Force on Organ Transplantation
April 28, 1986	Final Meeting of the National Task Force on Organ Transplantation
July 14, 1986	Final Report of the National Task Force on Organ Transplantation is Released to the Public
September 30, 1986	United Network for Organ Sharing Contract is Awarded by the Health Resources and Services Administration
October 17, 1986	Medicare Program Criteria for Medicare Coverage of Heart Transplants; Proposed Notice Published in the Federal Register
April 6, 1987	Medicare Program; Criteria For Medicare Coverage of Heart Transplants; Final Notice Published in the Federal Register
January 19, 1988	Medicare Program: Medicare Coverage of Immunosuppressive Drugs; Proposed Rule, Federal Register

Table 1-7 (continued)

Key Events in Organ Transplantation

March 1, 1988	Medicare and Medicaid Programs; Organ Procurement Organizations and Organ Procurement Protocols; Final Rule, Federal Register
March 2, 1988	Medicare Program: Payment for Kidneys Sent to Foreign Countries or Transplanted in Non-Medicare Beneficiaries; Proposed Rule, Federal Register
March 18, 1988	United Network for Organ Sharing Policies and Rationale for Transplantation of Organs for Foreign Nationals and Exportation of Organs Outside the United States, General Notice, Federal Register

Finally, although not listed in Table 1-7, but very important, is passage of the Medicare Catastrophic Coverage Act by Congress in June, 1988.

If one were to thoroughly review the foregoing legislation, it would become evident that kidney transplantation greatly benefitted from the rapid emergence of extrarenal transplantation procedures as clinical realities. For example, the initial Congressional hearings held by then Congressman Albert R. Gore, Jr. in April, 1983 focused largely on the need for pediatric liver donors, as did the Surgeon General's Workshops held in Millwood, Virginia (Gunby, 1983:2103; Hearings before the Subcommittee on Investigations and Oversight, 1984; Iglehart, 1983:123; 1984:864; Kutner, 1987:23; White, 1985:109). Not surprisingly, this fixation on pediatric donors was beneficial to kidney transplantation as numerous efforts were initiated to educate both the public and professionals as to the need for organ donors. Subsequently, the overall supply of donors improved and the number of kidney transplants performed annually began to increase. For the very first time in the history of the End-Stage Renal Disease Program it was felt that very positive changes were in store for the future of the Program. The goal was to effect a net reduction in the number of dialysis patients by transplanting an ever-increasing number of patients. As noted by Eggers (1988:223), this has occurred for some age groups. However the ESRD population continues to grow, with elderly patients accounting for the largest growth.

Nonetheless, as described by Eggers (1988:223), transplantation will have the effect of slowing the rate of increase of overall ESRD Program expenditures. As more patients are transplanted and continue to survive with functioning grafts, expenditures will be moderated.

Eggers (1988:223) argues that "The combined effect of increasing numbers of transplantations and increased survival rates of grafts is resulting in a shift from what was previously a population of patients on dialysis to a population increasingly composed of patients with functioning grafts." This is most significant for persons younger than 55, since by the end of 1985, 31 percent of enrollees in the Medicare End-Stage Renal Disease Program in this age group had functioning grafts. Moreover, among patients younger than 25, Eggers (1988:223) notes that the number of patients on dialysis has already begun to decline.

As alluded to above, these changes are unlikely to render the ESRD Program a nondialysis program. The patient population continues to grow, and the fastest growing segment of the population, as already noted, is those patients age 65 and over, for which transplantation will have little effect. For example, in 1985 there were 10,285 new patients with ESRD in this age group, but only 57 persons aged 65 and over received a transplant. The ESRD patient population, as Eggers (1988:223) observes, is divided between patients under 55 years of age who are increasingly likely to receive transplants, and those 55 and older who are almost exclusively on dialysis.

ESRD Program Statistics

As the foregoing suggests, important changes are occurring in the composition of the ESRD patient population. To provide an appropriate context for this report, it is important that these changes, as well as the trends that accompany them, are documented. Much of the relevant data pertaining to the ESRD program, including incidence and enrollment, patient treatment modalities, reimbursement and utilization, providers of renal care and patient survival, are summarized annually in the Health Care Financing Administration's (HCFA) Annual Report to Congress (see HCFA, 1987; 1988). These data are selectively reviewed below, based on HCFA's 1986 End-Stage Renal Disease Research Report. It should be noted that much of the text that follows, as well as the tables, are taken verbatim from a draft of the 1986 Report.

Program Incidence

Program incidence is defined as the number of new ESRD patients that enroll in the ESRD Program during the most recent year. The 1986 Annual Report includes data through 1985.

Table 1-8 summarizes the age, size, race, and primary disease diagnosis distribution of new ESRD patients for the period 1980-1985. In 1980, 18,404 new patients were added to the Medicare rolls, while in 1985, 28,944 patients were added. The average annual increase, as indicated, was 9.5 percent. The age group with the largest percentage increase was that of persons 65-74 years of age (12.8%) and persons 75 years of age and over (20.8%).

Over the period 1980-85, the percentage increase in males and females was similar (8.9% versus 10.2%). This was also true of blacks and whites (10.9% and 9.7%). However, as is apparent in Table 1-8, sizable increases occurred among Asians (59.1%) and American Indians (31.6%) although these increases may be due to improved reporting on various HCFA forms.

Annual rates of growth exceeded 20 percent for persons whose renal failure was attributed to diabetes, glomerulonephritis, and hypertension. Once again, however, these increases may be in part due to better data reporting.

Table 1-8

Medicare End Stage Renal Disease Program Incidence
Age, Sex, Race, and Primary Diagnosis: 1980-85

Age, Sex and Race	1980	1981	1982	1983	1984	1985	Average Annual Percent Change	1984-85 Percent Change
			Number of New Enrollees					
Total	18,404	19,307	21,815	24,991	26,297	28,944	9.5	10.1
Age								
Under 15 yr	374	336	414	382	433	423	2.5	-2.3
15-24 yr	1,091	1,115	1,170	1,097	1,151	1,183	1.6	2.8
25-34 yr	2,092	2,189	2,458	2,450	2,615	2,684	5.1	2.6
35-44 yr	2,244	2,368	2,595	2,832	3,010	3,360	8.4	11.6
45-54 yr	3,167	3,234	3,529	3,734	3,841	4,191	5.8	9.1
55-64 yr	4,346	4,713	5,263	5,747	6,230	6,818	9.4	9.4
65-74 yr	3,746	3,939	4,574	5,982	6,068	6,828	12.8	12.5
75 yr or over	1,344	1,413	1,812	2,767	2,949	3,457	20.8	17.2
Sex								
Male	10,316	10,725	12,070	13,754	14,568	15,814	8.9	8.6
Female	8,088	8,582	9,745	11,237	11,729	13,130	10.2	11.9
Race								
Asian	48	126	308	310	378	489	59.1	29.4
Black	4,830	5,000	5,932	7,118	7,391	8,091	10.9	9.5
White	12,474	13,226	15,163	17,009	18,045	19,809	9.7	9.8
American Indian	67	127	194	257	259	264	31.6	1.9
Other/unknown	985	828	218	297	224	291	-21.6	29.9
Diagnosis								
Diabetes	2,225	3,620	4,989	5,867	7,047	8,019	29.2	13.8
Glomerulonephritis	2,208	3,437	5,093	5,486	5,780	6,126	22.6	6.0
Hypertension	2,453	3,918	5,368	5,709	6,354	7,097	23.7	11.7
Polycystic Kidney Disease	602	832	1,012	1,055	1,057	1,139	13.6	7.8
Other/unknown	10,916	7,500	5,353	6,874	6,059	6,563	-9.7	8.3

SOURCE: Health Care Financing Administration, Bureau of Data Management and Strategy: Data from the Program Management and Medical Information System, 1980-85, August 1987 update.

In 1985, the rate of increase in enrollees was 10.1 percent. The increase was larger for persons 75 years of age or over (17.2%), while there was a decrease of 2.3 percent in cases for persons less than 15 years of age.

Of the 28,944 new Medicare ESRD beneficiaries in 1985, 35.5 percent were 65 years of age or over; 54.6 percent were male; 68.4 percent were white; and 27.7 percent had diabetes reported as the primary cause of renal failure.

Table 1-9 summarizes ESRD program incidence expressed in terms of rates per million population. Overall, during the period 1980-85, the number of enrollees per million population increased from 81 to 121 for an annual percentage change of 8.4 percent. Incidence rates were clearly related to age, with patients 75 years and over having the greatest annual increase. The incidence rate for males is greater than that of females, with blacks clearly having the highest incidence of all (281 per million), followed by American Indians (171 per million). Polycystic kidney disease is the least common cause of renal failure among new enrollees. Interestingly, between 1980 and 1985 there has been a three-fold increase in the incidence of diabetes among new enrollees.

Program Enrollment

Tables 1-10 and 1-11 summarize various characteristics--age, sex, race and diagnosis--of dialysis patients. Table 1-10 provides the numbers of patients, and Table 1-11 summarizes them per million population. Because of the increased program incidence described previously, growth in the dialysis patient population has been greatest for persons 65 years of age or over. In 1980, persons 65 years of age or over accounted for 23.5 percent of the total

Table 1-9

Medicare End Stage Renal Disease Program Incidence Rates Per Million Population by Age, Sex, Race, and Primary Diagnosis: 1980-85

Age, Sex and Race	1980	1981	1982	1983	1984	1985	Average Annual Percent Change	1983-84 Percent Change
	Number of Enrollees Per Million Population							
Total	81	84	94	107	111	121	8.4	8.9
Age								
Under 15 yr	7	7	8	7	8	8	2.2	-2.7
15-24 yr	26	26	28	27	29	30	3.1	4.1
25-34 yr	56	56	62	61	64	64	2.7	-0.1
35-44 yr	87	90	92	96	98	106	4.0	7.7
45-54 yr	139	143	157	167	171	186	5.9	8.3
55-64 yr	200	215	238	258	279	305	8.9	9.3
65-74 yr	239	247	282	362	362	402	10.9	10.8
75 yr or over	134	137	170	252	261	300	17.5	14.8
Sex								
Male	93	96	107	121	127	136	7.8	7.2
Female	69	73	82	93	97	107	9.1	10.9
Race								
Asian	13	34	83	83	101	129	57.5	28.0
Black	176	181	212	252	260	281	9.8	8.3
White	64	67	76	85	89	97	8.6	8.6
American Indian	46	86	76	170	170	171	30.3	0.8
Other/unknown	--	--	--	--	--	--	--	--
Diagnosis								
Diabetes	10	16	22	25	30	34	28.2	12.6
Glomerulo-nephritis	10	15	22	23	24	26	21.4	4.6
Hypertension	11	17	23	24	27	30	22.5	10.5
Polycystic Kidney Disease	3	4	4	5	4	5	12.5	6.6
Other/unknown	48	33	23	29	26	27	-10.6	7.1

SOURCE: Health Care Financing Administration, Bureau of Data Management and Strategy: Data from the Program Management and Medical Information System, 1980-85, August 1987 update; and Census Population Estimates.

Table 1-10

Medicare End Stage Renal Disease Program Enrollment for Dialysis Patients by Age, Sex, Race, and Primary Diagnosis: 1980-85

Age, Sex and Race	1980	1981	1982	1983	1984	1985	Average Annual Percent Change	1984-8 Percen Change
Total	56,321	62,652	69,580	77,167	83,086	88,510	9.6	6.5
Age								
Under 15 yr	676	706	792	814	803	756	2.3	-5.9
15-24 yr	3,107	3,270	3,362	3,268	3,188	3,113	0.0	-2.4
25-34 yr	6,563	7,175	7,735	7,998	8,206	8,373	5.0	2.0
35-44 yr	7,820	8,587	9,376	10,368	11,015	11,670	8.3	5.9
45-54 yr	10,817	11,749	12,623	13,336	14,100	14,686	6.3	4.2
55-64 yr	14,116	15,879	17,727	19,416	20,888	22,141	9.4	6.0
65-74 yr	10,224	11,639	13,465	15,975	17,794	19,495	13.8	9.6
75 yr or over	2,998	3,647	4,500	5,992	7,092	8,276	22.5	16.7
Sex								
Male	30,983	34,198	37,731	41,597	44,636	47,102	8.7	5.5
Female	25,338	28,454	31,849	35,570	38,450	41,408	10.3	7.7
Race								
Asian	140	258	480	655	825	1,052	49.7	27.5
Black	16,452	18,530	21,096	24,075	26,567	28,890	11.9	8.7
White	36,688	40,643	44,948	49,291	52,585	55,438	8.6	5.4
American Indian	149	183	326	505	631	712	36.7	12.8
Other/unknown	2,892	3,038	2,730	2,641	2,478	2,418	-3.5	-2.4
Diagnosis								
Diabetes	4,299	6,164	8,562	10,853	13,486	15,811	29.8	17.2
Glomerulonephritis	8,549	10,419	13,137	15,529	17,466	19,173	17.5	9.8
Hypertension	6,972	9,187	12,062	14,584	16,864	18,977	22.2	12.5
Polycystic Kidney Disease	2,631	3,099	3,636	4,060	4,352	4,619	11.9	6.1
Other/unknown	33,870	33,783	32,183	32,141	30,918	29,930	-2.4	-3.2

SOURCE: Health Care Financing Administration, Bureau of Data Management and Strategy: Data from the Program Management and Medical Information System, 1980-85, August 1987 update.

Table 1-11

Medicare End Stage Renal Disease Program Dialysis Enrollment Per Million Population by Age, Sex, Race, and Primary Diagnosis: 1980-85

Age, Sex and Race	Number of Enrollees Per Million 1980	1981	1982	1983	1984	1985	Average Annual Percent Change	1984-85 Percent Change
Total	248	273	300	330	352	371	8.4	5.4
Age								
Under 15 yr	13	14	15	16	16	15	2.0	-6.2
15-24 yr	73	78	81	80	80	79	1.5	-1.1
25-34 yr	175	184	196	199	201	199	2.6	-0.7
35-44 yr	303	325	333	353	359	367	3.9	2.2
45-54 yr	476	520	563	596	629	650	5.8	3.4
55-64 yr	649	723	802	873	936	991	8.9	5.9
65-74 yr	653	731	831	968	1,063	1,147	11.9	7.9
75 yr or over	298	353	422	546	628	718	19.2	14.3
Sex								
Male	281	307	335	366	389	405	7.6	4.3
Female	217	241	267	296	317	338	9.3	6.7
Race								
Asian	39	71	130	176	219	277	48.2	26.1
Black	601	670	755	853	933	1,004	10.8	7.6
White	188	207	226	246	260	271	7.5	4.3
American Indian	101	123	218	334	414	462	35.4	11.6
Other/unknown	--	--	--	--	--	--	--	--
Diagnosis								
Diabetes	19	27	37	46	57	66	28.5	16.0
Glomerulonephritis	38	45	57	66	74	80	16.4	8.6
Hypertension	31	40	52	62	71	79	21.0	11.3
Polycystic Kidney Disease	12	14	16	17	18	19	10.8	5.0
Other/unknown	149	147	139	137	131	125	-3.4	-4.2

SOURCE: Health Care Financing Administration, Bureau of Data Management and Strategy: Data from the Program Management and Medical Information System, 1980-85, August 1987 update.

dialysis patient population, increasing to 31.4 percent in 1985. As noted previously, the transplantation effect is apparent for patients in the younger age groups. For the under age 15 group, dialysis population growth peaked in 1983, and declined in both 1984 and 1985. For persons 15 to 24 years of age, the dialysis population peaked in 1982 and has been followed by three consecutive years of decreases.

In 1985, 53.2 percent of the Medicare dialysis population were male; 62.6 percent were white persons, and 17.9 percent were persons for whom diabetes was reported as the primary cause of renal failure.

As shown in Table 1-11, overall dialysis patient population enrollees increased from 248 per million in 1980 to 371 per million in 1985. The number of enrollees per million was greatest for persons 65 years of age and over and lowest for persons under 15 years of age. Blacks and Indians had the highest rates per million, with diabetes being the primary cause of renal failure.

As the number of transplant patients surviving with a functioning graft increases annually, it is of interest to examine them as a group separate from dialysis. In Tables 1-12 and 1-13 data are provided on patients with functioning grafts according to age, sex, race, and primary disease diagnosis. In contrast to the dialysis population, persons with a functioning graft came largely from the younger age group. In 1980, 90.8 percent of the persons with a functioning graft were 55 years of age or less, compared with 88.2 percent in 1985.

In 1985, 63.0 percent of the Medicare ESRD population with a functioning graft were male; 78.1 percent were white persons, and 14.9 percent were persons for whom diabetes was reported as the primary cause of

Table 1-12

Medicare End Stage Renal Disease Program Enrollment by Age, Sex, Race, and Primary Diagnosis for Functioning Graft Patients: 1980-85

Age, Sex and Race	1980	1981	1982	1983	1984	1985	Average Annual Percent Change	1984-85 Percent Change
Total	7,772	8,974	10,862	13,198	16,221	19,610	20.3	20.9
Age								
Under 15 yr	260	284	349	434	550	664	20.6	9.3
15-24 yr	1,208	1,304	1,490	1,725	1,930	2,162	12.7	9.4
25-34 yr	2,301	2,694	3,174	3,816	4,593	5,276	17.8	16.1
35-44 yr	1,830	2,205	2,790	3,432	4,348	5,424	24.5	21.6
45-54 yr	1,455	1,654	2,000	2,444	3,010	3,764	23.0	23.5
55-64 yr	646	748	946	1,197	1,588	2,022	28.8	31.3
65-74 yr	70	82	110	147	197	290	39.7	50.3
75 yr or over	2	3	3	3	5	8	38.0	87.5
Sex								
Male	4,724	5,528	6,777	8,261	10,185	12,358	21.2	21.3
Female	3,048	3,446	4,085	4,937	6,036	7,252	18.9	20.1
Race								
Asian	17	21	60	126	201	259	72.4	28.9
Black	1,187	1,381	1,767	2,257	2,870	3,585	24.7	24.9
White	6,169	7,043	8,523	10,333	12,725	15,325	20.0	20.4
American Indian	29	107	120	139	140	170	42.4	21.4
Other/unknown	370	422	392	343	285	271	-6.0	-4.9
Diagnosis								
Diabetes	533	721	1,086	1,531	2,112	2,910	40.4	37.8
Glomerulonephritis	1,923	2,245	2,896	3,765	4,934	6,100	26.0	23.6
Hypertension	468	575	833	1,154	1,529	1,983	33.5	29.7
Polycystic Kidney Disease	259	306	439	606	847	1,059	32.5	25.0
Other/unknown	4,589	5,127	5,608	6,142	5,799	7,558	10.5	11.2

SOURCE: Health Care Financing Administration, Bureau of Data Management and Strategy; Data from the Program Management and Medical Information System, 1980-85; August 1987 update.

Table 1-13

Medicare End Stage Renal Disease Program Enrollment Per Million Population for Patients with a Functioning Graft by Age, Sex, Race, and Primary Diagnosis: 1980-85

Age, Sex and Race	Number of Patients Per Million						Average Annual Percent Increase	1984 Perc Incr
	1980	1981	1982	1983	1984	1985		
Total	34	39	47	56	69	82	19.2	19.
Age								
Under 15 yr	5	6	7	8	11	13	20.3	8.
15-24 yr	28	31	36	42	48	55	14.3	10.
25-34 yr	61	69	81	95	112	126	15.2	13.
35-44 yr	71	83	99	117	142	171	19.4	17.
45-54 yr	64	73	89	109	134	167	23.1	22.
55-64 yr	30	34	43	54	71	91	28.2	31.
65-74 yr	4	5	7	9	12	17	37.4	48.
75 yr or over	0	0	0	0	0	1	34.2	83.
Sex								
Male	43	50	60	73	89	106	20.0	19.
Female	26	29	34	41	50	59	17.8	19.
Race								
Asian	5	6	16	34	53	68	70.7	27.
Black	43	50	63	80	101	125	23.5	23.
White	32	36	43	52	63	75	18.8	19.
American Indian	20	72	80	92	92	110	41.0	20.
Other/unknown	--	--	--	--	--	--	--	--
Diagnosis								
Diabetes	2	3	5	7	9	12	39.0	36.
Glomerulonephritis	8	10	12	16	21	26	24.7	22.
Hypertension	2	3	4	5	6	8	32.2	28.
Polycystic Kidney Disease	1	1	2	3	4	4	31.2	23.
Other/unknown	20	22	24	26	29	32	9.4	10.

SOURCE: Health Care Financing Administration, Bureau of Data Management and Strategy: Data from the Program Management and Medical Information System, 1980-85; August 1987 update.

renal failure. In this regard, it is noteworthy that, in 1980, 6.9 percent of patients with functioning grafts had diabetes as their primary cause of renal failure.

In terms of the rates per million population, the ESRD functioning graft population has increased from 34 per million in 1980 to 82 per million in 1985, a 19.2 percent annual increase. In 1985, those persons 34-44 years of age, and 45-54 years of age had the highest rate per million population (171 and 167 per million, respectively). The rate was higher for males (106 per million) than for females (59 per million) and was higher for black persons (125 per million) than for white persons (75 per million).

Patient Treatment Trends

As was apparent from previous tables, significant changes are occurring within the ESRD patient population according to ESRD treatment modality. Table 1-14 summarizes the numbers of patients according to dialysis modality for the period 1980-87. As indicated, there has been an 88 percent increase in the size of the patient population. The in-unit total number of patients has increased by 79.3 percent, while the home total increased by 138.7 percent. Although there has been a 24 percent decline in home hemodialysis patient population, and a 72.5 percent decline in the peritoneal dialysis patient population, there has been a 549.5 percent increase in the continuous ambulatory peritoneal dialysis patient population. Also, there has been a 195.7 percent increase in the in-unit self-hemodialysis patient population.

In 1987, 81.4 percent of dialysis patients were on in-unit dialysis, compared with 85.4 percent in 1980. In 1987, of the home patients, 19.6 percent were on home hemodialysis, while in 1980, 61.5 percent of the home

Table 1-14

Annual Distribution of Kidney Dialysis Patients by Treatment Modality (1980-87)

Treatment Modality	1980	1981	1982	1983	1984	1985	1986	1987	Percent Change
Total Dialysis Patients	52,364	58,924	65,765	71,987	78,483	84,797	90,886	98,432	88.0
In-Unit Total	44,703	49,450	54,032	58,342	63,245	68,394	73,800	80,149	79.3
Staff Assisted Hemodialysis	42,501	46,980	51,499	55,554	60,563	65,515	71,161	77,845	83.2
Staff Assisted Peritoneal	900	937	874	742	584	583	509	440	-48.9
Self-Hemodialysis	770	1,031	1,060	1,475	1,611	1,726	1,595	1,507	195.7
Self-Peritoneal	11	7	11	3	6	1	1	0	-100.0
Self-Dialysis Training (ALL)	521	495	588	568	481	569	534	357	-31.5
Home Total	7,661	9,474	11,733	13,645	15,238	16,403	17,086	18,283	138.7
Hemodialysis	4,715	4,481	4,394	4,323	4,125	3,983	3,675	3,582	-24.0
Peritoneal	612	646	816	790	259	231	191	168	-72.5
CAPD	2,334	4,347	6,523	8,532	9,995	11,236	11,913	12,825	549.5
CCPD	0	0	0	0	859	953	1,307	1,708	N/A

patients were on home hemodialysis. Today, over 70 percent of the home patients are on continuous ambulatory peritoneal dialysis, compared with 30.5 percent in 1980.

The total number of kidney transplants performed per year is shown in Table 1-15, with an indication of the total number of living kidney transplant recipients (estimated) at year end for the years 1963 through 1988. As indicated, with the exception of a few years, there has been a steady increase in the number of transplants performed annually. Concomitantly, the number of patients that are alive with functioning grafts has increased. Today, it is estimated that over 42,000 kidney transplant recipients are alive with functioning grafts, although not all of these patients are Medicare-eligible. Eggers (1988:223) estimates that 50 percent of all living transplant recipients retain Medicare eligibility.

Table 1-16 summarizes the annual distribution of kidney transplants performed according to the source of donor organ. In 1977, nearly 38 percent of all kidney transplants were performed using a living-related donor. In 1988, only 20.2 percent of all transplant recipients had a relative as the donor organ source. Because of the improved success rates of cadaveric kidney transplants, controversy has emerged as to the appropriateness of living-related kidney transplantation (Burley and Stiller, 1985:123; Spital et al., 1987:396; Spital and Spital, 1987:49; 1985:1297; News, 1987:9; Tapson, 1985:13; Patel, 1988:1068). For example, some transplant surgeons, including Starzl, argue that donor nephrectomy poses an unreasonable risk for the living donor. He finds this unacceptable and, consequently, the University of Pittsburgh performs very few living-related donor kidney transplants.

Table 1-15

Total Number of Kidney Transplants by Year and Number of Living Transplant Recipi

Year	Total Number of Kidney Transplants by Year	Total Number of Living Transplant Recipients*
1951-62	75	N/A
1963	163	78
1964	239	183
1965	305	305
1966	338	457
1967	448	666
1968	676	1,039
1969	838	1,441
1970	1,091	2,175
1971	1,616	3,784
1972	1,993	5,134
1973	3,017	6,436
1974	3,190	7,670
1975	3,730	9,079
1976	3,504	10,150
1977	3,973	11,353
1978	3,949	12,316
1979	4,189	13,772
1980	4,697	17,578
1981	4,883	19,124
1982	5,358	21,248
1983	6,112	23,755
1984	6,968	28,319
1985	7,695	32,375
1986	8,976	36,247
1987	8,967	39,585
1988	9,123	42,855

* Not available for 1951-1962. Estimated for 1963-1988.

Table 1-16

Annual Distribution of Kidney Transplants by Source of Donor Organ (1977-1988)

	Type of Kidney Transplant				
	Living-Related Donor		Cadaveric Donor		
Year	Number	Percent	Number	Percent	Total
1977	1,495	37.6	2,488	62.4	3,973
1978	1,172	29.7	2,777	70.3	3,949
1979	1,186	28.3	3,003	71.7	4,189
1980	1,275	27.1	3,422	72.9	4,697
1981	1,458	29.9	3,425	70.1	4,883
1982	1,677	31.3	3,691	68.7	5,358
1983	1,784	29.2	4,328	70.8	6,112
1984	1,704	24.5	5,264	75.5	6,968
1985	1,876	24.4	5,819	75.6	7,695
1986	1,887	21.0	7,089	79.0	8,976
1987	1,907	21.3	7,060	78.7	8,967
1988*	1,845	20.2	7,278	79.8	9,123

*United Network for Organ Sharing data.

Alternatively, Najarian and colleagues (see Roberts, et al., 1988:26) argue that there is a shortage of cadaveric donors, and the demand for kidney transplantation is great. Therefore, to offer the maximum number of ESRD patients the transplant option, they feel it is perfectly acceptable to use living-related donors. Moreover, they note that a more compelling reason to use living-related donor allografts is the improved survival of grafts and patients receiving grafts from living-related donors. They further argue that if the recipients of living-related donor grafts had instead received cadaveric grafts, an additional 241 recipients would have died in the first 10 years of their series. Not surprisingly, therefore, the University of Minnesota is among the leading living-related donor kidney transplant centers in the United States. In this regard, it is noteworthy that Dr. Richard L. Simmons, chairman of the Department of Surgery at the University of Pittsburgh, has recently initiated a living-related donor kidney transplant service. Pittsburgh now has three separate kidney transplant services--two devoted to cadaveric grafts and one to living-related grafts.

In a review of 16 published reports on the surgical mortality of living kidney donors, Bay and Hebert (1988:272) found that of 2,495 donors described in the reports, only three died from events that were thought to be related to the surgical procedure. Thus, the mortality rate of donor nephrectomy from these combined series is 0.1 percent. In a survey of the 12 largest renal transplant centers performing living donor transplantation who collectively performed 5,698 living donor transplants, two donor deaths related to nephrectomy were reported, with an overall surgical mortality of 0.04 percent. In short, the mortality risk of kidney donation is about one death per 1,600 donors.

Eggers (1988:223) has described the characteristics of Medicare beneficiaries who received kidney transplants in 1985 (see Table 1-17). Clearly, there is an age difference between patients who receive cadaveric grafts and those receiving grafts from living-related donors. The recipients of kidneys from cadavers were seven years older, on average, than the recipients of kidneys of living-related donors (38.8 vs. 31.5 years). This difference is also evident in the percentage of transplants from living-related donors within each age group. Almost half (47%) of transplant recipients up to the age of 14 received a kidney from a living-related donor. This percentage declined with age, to six percent among recipients 65 to 74 years of age. Blacks accounted for 21 percent of patients who received transplants (1437 of 6910), a percentage considerably lower than their 33 percent share of all patients with end-stage renal disease. Blacks accounted for 24 percent of the recipients of kidneys, but only 12 percent of recipients of transplants from living related donors. No significant differences were found between the type of donor and the patient's sex or the primary cause of renal failure.

There is little question that the demand for kidney transplantation is tremendous. In Table 1-5, a monthly listing of the number of patients on the UNOS kidney transplant recipient waiting list was provided. In Table 1-18 this listing is enhanced by providing an indication of the number of patients who have been on the list for the period December, 1980 through May, 1989. Clearly, as shown, with the exception of 1983, there has been a steady increase in the percent of the dialysis patient population that is awaiting a kidney transplant.

Table 1-17

Characteristics of Medicare Beneficiaries Receiving Transplants, According to Type of Donor, 1985

	Transplants From Cadavers		Transplants From Living Related Donors		All Transplants*	
Characteristic	Number	Percent	Number	Percent	Number	(% Living Rela
Age (year)						
0-14	187	4	168	10	360	47
15-24	590	12	327	20	936	35
25-34	1182	23	537	32	1771	30
35-44	1435	28	348	21	1830	19
45-54	1102	22	208	13	1339	16
55-64	534	11	63	4	617	10
65-74	50	1	3	0	53	6
≥ 75	4	0	0	0	4	0
Mean age	38.8		31.5		37.0	
Sex						
Male	3245	64	969	59	4321	22
Female	1839	36	685	41	2589	26
Race						
White	3666	72	1387	84	5180	27
Black	1197	24	206	12	1437	14
Other/unknown	221	4	61	4	293	21
Primary Disease						
Diabetes	912	18	320	19	1268	25
Glomerulonephritis	1605	32	572	35	2235	26
Hypertension	684	13	125	8	832	15
Other/unknown	1882	37	637	39	2575	37
Total	5084	100	1654	100	6910	24

SOURCE: Eggers, 1988:225

* Includes transplants in which the donor type was unspecified.

Table 1-18

Number of Patients Awaiting Kidney Transplants (1980-89)

Year	Percent Number	Increase	Percent of Dialysis Population
1980	5,072	N/A	9.7
1981	5,773	13.8	9.8
1982	6,720	16.4	10.2
1983	7,176	6.2	10.0
1984	8,562	19.9	10.9
1985	9,791	14.4	11.5
1986	10,605	8.3	11.7
1987	11,872	11.9	12.1
1988	13,703	15.4	N/A
1989	14,949	9.1	N/A

SOURCES: Health Care Financing Administration, Baltimore, Maryland, and the United Network for Organ Sharing, Richmond, Virginia.

N/A = not available.

Reimbursement

Over the years, the reimbursement and utilization data available through the Health Care Financing Administration have steadily improved. Compiled from various HCFA reports, Tables 1-19 and 1-20 display reimbursement, enrollment, per capita reimbursement, and type of service figures for the End-Stage Renal Disease Program. As indicated, in 1987, approximately 2.6 billion dollars were spent to care for about 127,900 patients with ESRD (dialysis as well as transplant recipients with functioning grafts). Reimbursements per enrollee totaled approximately $20,200.

Eggers has recently updated various data contained in Tables 1-19 and 1-20. These are summarized in Table 1-21. Eggers has adjusted the figures upward to reflect a downward bias in the raw numbers. For example, in the pre-prospective payment era, the inpatient numbers reflected average per diems and thus tended to underestimate the ESRD cases by not including the cost of inpatient dialysis. In the post-prospective payment era, the inpatient numbers fail to include pass-through amounts, that is, medical education, capital, and kidney acquisition. Table 1-21 adjusts the figures in Tables 1-19 and 1-20 accordingly.

Clearly, regardless of what tables are used, there has been a continued increase in total expenditures, however, the actual reimbursements per enrollee have been relatively unchanged. In short, increased program expenditures are due to increased patient enrollments.

The type of service expenditures summarized in Table 1-20 are interesting. In 1974, outpatient expenditures accounted for 59.2 percent of total expenditures, and inpatient expenditures accounted for 28.4 percent of total expenditures. By 1987 the comparable percentages for outpatient and

Table 1-19

Medicare Reimbursements, by Enrollees and Per Capita Reimbursements for Persons With End-Stage Renal Disease: 1974-1987

	Reimbursements		Enrollment		Reimbursement Per Enrollee	
YEAR	Amount in Millions	Percent Change	Number Thousands	Percent Change	Amount	Percent Change
1974	$ 228.5	--	16.0	--	$14,300	--
1975	361.1	58.0	22.7	41.9	15,900	11.2
1976	512.2	41.8	28.9	27.3	17,720	11.4
1977	641.3	25.2	34.8	20.4	18,420	3.9
1978	800.0	24.7	43.5	25.0	18,390	-0.2
1979	1,010.7	26.3	54.4	25.1	18,579	1.0
1980	1,252.2	23.8	61.9	13.8	20,229	8.9
1981	1,476.2	17.9	70.4	13.7	20,969	3.7
1982	1,661.9	12.6	77.9	10.7	21,321	1.7
1983	1,898.4	14.2	86.5	11.0	21,891	2.7
1984	2,002.9	5.5	92.8	7.3	21,051	-3.8
1985	2,126.1	6.2	107.1	15.4	19,851	-5.7
1986	2,403.7	13.1	117.1	9.3	20,257	2.0
1987	2,585.2	7.6	127.9	9.2	20,213	-0.2

Table 1-20

Medicare End-Stage Renal Disease Reimbursements, by Type of Service: 1974-1987

		TYPE OF SERVICE			
Year	Total (in Millions)	Outpatient (in Millions)	Inpatient (in Millions)	Physician/ Supplier (in Millions)	Home Health/Skilled Nursing Facilities (in Millions)
1974	$ 228.5	$ 135.5	$ 64.9	$ 27.6	$ 0.5
1975	361.1	205.2	99.1	55.7	1.1
1976	512.2	289.6	136.3	84.5	1.8
1977	641.3	368.0	164.1	106.8	2.4
1978	800.0	453.0	208.9	135.2	2.9
1979	1,010.7	557.9	267.9	181.2	3.7
1980	1,252.2	665.8	343.6	283.3	4.5
1981	1,476.2	732.5	435.1	303.3	5.4
1982	1,661.9	781.6	519.5	354.3	6.5
1983	1,898.4	854.8	624.8	408.9	9.9
1984	2,002.9	867.4	732.2	390.5	12.8
1985	2,126.1	829.5	822.2	458.4	16.0
1986	2,403.7	979.8	895.4	515.7	16.8
1987	2,585.2	1,053.2	938.0	577.0	17.0

Table 1-21

Adjusted ESRD Program Costs and Number of Beneficiaries: 1974-1987

Year	Adjusted Total (in Millions)	Adjusted Inpatient (in Millions)	Outpatient (in Millions)	Physician/ Supplies (in Millions)	Other (in Millions)	Number of Beneficiaries
1974	$ 239.7	$ 76.1	$ 135.5	$ 27.6	$ 0.5	15,993
1975	378.2	116.2	205.2	55.7	1.1	22,674
1976	535.7	159.8	289.6	84.5	1.8	28,941
1977	669.6	192.4	368.0	106.8	2.4	34,778
1978	836.1	245.0	453.0	135.2	2.9	44,193
1979	1,057.2	314.4	557.9	181.2	3.7	52,237
1980	1,307.6	399.1	665.8	238.3	4.4	60,119
1981	1,542.5	501.2	732.6	303.3	5.4	67,550
1982	1,742.7	600.3	781.6	354.3	6.5	76,385
1983	1,989.1	715.5	854.8	408.9	9.9	86,379
1984	2,083.4	812.7	867.4	390.5	12.8	95,462
1985	2,217.7	912.9	829.9	458.9	16.0	104,629
1986	2,515.3	1,001.9	978.1	518.5	16.8	114,039
1987	2,763.5	1,066.8	1,079.0	599.9	17.8	123,743

Source: Paul Eggers, Ph.D., Office of Research, Health Care Financing Administration, Baltimore, Maryland inpatient expenditures were 40.7 and 36.2 percent, respectively. According to Eggers (personal communication, April 4, 1989), the major reason for the shift in reimbursement percentages is that dialysis costs were capped, and even reduced, whereas inpatient costs were the fastest rising part of the health care industry. Patient case-mix has probably played a minor role. It is interesting to note, however, that aged and disabled Medicare beneficiaries have experienced large reductions in total inpatient days (approximately 30 percent) since the introduction of prospective payment. The reduction in days for ESRD patients has been about 10 percent, this being totally a length of stay effect, with no change in discharge rates.

The percentage of total expenditures associated with home health/skilled nursing facility care has tripled between 1974 and 1987, from 0.2 percent to 0.6 percent. This quite naturally reflects the "aging" of the ESRD patient population.

Finally, physician/supplier services have also increased between 1974 and 1987, from 12.1 percent to 22.3 percent, perhaps reflecting the decline in home dialysis in the United States.

To add additional perspective, Eggers has provided data on total Medicare Program expenditures. These are summarized in Table 1-22 and should be compared with the data in Table 1-21.

Utilization

In 1985 there were 107,697 Medicare end-stage renal disease beneficiaries who were eligible for Medicare benefits for at least part of the year. In the following analysis, inpatient utilization will be considered separately for each

Table 1-22

Total Medicare Program Expenditures: 1974-87

Year	Total Expenditures (in Millions)	Part A Hospital Insurance (in Millions)	Part B Supplementary Medical Insurance (in Millions)	Expenditures Per Person
1974	$11,453.0	$ 8,304.0	$ 3,149.0	$ 512.0
1975	14,309.0	10,381.0	3,928.0	624.0
1976	17,175.0	12,357.0	4,818.0	716.0
1977	21,309.0	15,175.0	6,134.0	819.0
1978	24,803.0	17,549.0	7,254.0	919.0
1979	28,745.0	20,132.0	8,613.0	1,050.0
1980	34,737.0	24,268.0	10,469.0	1,253.0
1981	41,698.0	29,140.0	12,558.0	1,497.0
1982	49,341.0	34,524.0	14,817.0	1,732.0
1983	57,070.0	39,408.0	17,662.0	1,913.0
1984	62,989.0	43,144.0	19,845.0	2,066.0
1985	68,600.0	46,652.0	21,948.0	2,267.0
1986	74,569.0	48,875.0	25,694.0	2,397.0
1987	81,265.0	50,796.0	30,469.0	2,478.0

Source: Paul Eggers, Ph.D., Office of Research, Health and Financing Administration, Baltimore, Maryland.

of several groups. These are: (1) persons on dialysis for the entire eligible years, (2) persons receiving a transplant in 1985, (3) persons receiving a transplant in a year prior to 1985, with a functioning graft through 1985, and (4) persons receiving a transplant in a year prior to 1985, with a kidney failure in 1985.

Persons on Dialysis for the Entire Eligible Year--

In 1985, the patient population on dialysis for the entire year numbered 82,422 and comprised 76.5 percent of all ESRD Medicare beneficiaries. Table 1-23 shows the distribution of these patients by age with the number of inpatient days and discharges associated with each group. This group is older than the total ESRD beneficiary population, with 56 percent 55 years of age or older. This dialysis population was hospitalized 100,122 times and accounted for 875,024 days of inpatient care. This utilization resulted in a discharge rate per 1,000 beneficiaries of 1,215, a days of care rate per 1,000 beneficiaries of 10,616, and an average length of stay per discharge of 8.7 days. With the exception of the youngest age group (0-14 years of age), there was a direct relationship between age and inpatient use. Compared to persons 15-24 years of age, persons 65 years of age and over were hospitalized 49 percent more often (949 discharges per 1,000 and 1,410 discharges per 1,000, respectively) and spent 97 percent more days as an inpatient (6,886 days per 1,000 and 13,568 per 1,000, respectively).

Persons Receiving a Transplant in 1985--

In 1985 there were 6,432 Medicare beneficiaries who received a kidney transplant. They accounted for 6.0 percent of the entire ESRD Medicare

Table 1-23

Discharge Rates for Medicare Dialysis Patients, by Days of Care Rates and Average Length of Stay: 1985

Age Group	Number of Patients	Number of Inpatient Days	Number of Inpatient Discharges	Discharges Per 1,000 Persons	Days Per 1,000 Persons	Average Length of Stay
Total	82,422	875,024	100,122	1,215	10,616	8.7
Under 15 yr	607	4,220	504	830	6,952	8.4
15-24 yr	2,753	18,957	2,613	949	6,886	7.3
25-34 yr	7,930	63,423	8,221	1,037	7,998	7.7
35-44 yr	10,951	91,596	11,486	1,049	8,364	8.0
45-54 yr	13,828	130,712	15,858	1,147	9,453	8.2
55-64 yr	20,954	221,515	25,628	1,223	10,571	8.6
65 yr +	21,399	344,601	35,812	1,410	13,568	9.6

SOURCE: Health Care Financing Administration, Bureau of Data Management and Strategy: Data from the Program Management and Medical Information System, 1985.

beneficiary population. The utilization of inpatient care by this population is shown in Table 1-24. In contrast to the dialysis population, the transplant population is much younger, with only 9.8 percent 55 years of age or older. Due to the transplant stay itself, and associated inpatient stays both before and after the transplant stay, this population experiences high hospitalization rates. The 6,432 persons in this group had 14,022 hospitalizations and were hospitalized for a total of 171,518 days. This utilization resulted in a discharge rate of 2,180 discharges per 1,000 beneficiaries and a days of care rate of 36,666 days per 1,000 beneficiaries. The lowest discharge and days of care rates were experienced by the youngest age group, persons 0-14 years of age. For the remaining persons there was not much difference in utilization by age group.

Persons Receiving a Transplant in a Year Prior to 1985, with a Functioning Graft Through 1985--

This group of persons represents the successful transplants from previous years. The 17,926 persons in this group accounted for 16.6 percent of all ESRD Medicare beneficiaries in 1985 (up from 13.6% in 1984). Table 1-25 presents the inpatient utilization for this patient population. The age distribution for this group is similar to that of persons transplanted in 1985. Fifty-six percent of these persons are between the ages of 25-44. The utilization of inpatient care is much less for this group than for either dialysis or transplant patients. This group was hospitalized 11,551 times for a total of 97,316 days. This utilization amounts to a discharge rate of 644 per 1,000 beneficiaries, and a days of care rate of 5,429 per 1,000 beneficiaries. With the exception of the youngest and oldest age groups, in which there

Table 1-24

Discharge Rates for Medicare Kidney Transplant Patients, by Days of Care Rates and Average Length of Stay: 1985

Number Age Group	Number of of Patients	Number of Inpatient Days	Discharges Inpatient Discharges	Days Per Per 1,000 Persons	Average 1,000 Persons	Length of stay
Total	6,432	171,518	14,022	2,180	26,666	12.2
Under 15 yr	313	6,778	545	1,741	21,655	12.4
15-24 yr	856	21,009	1,792	2,093	24,543	11.7
25-34 yr	1,632	43,684	3,681	2,256	26,767	11.9
35-44 yr	1,741	49,401	3,966	2,278	28,375	12.5
45-54 yr	1,259	33,678	2,696	2,141	26,750	12.5
55-64 yr	572	15,203	1,198	2,094	26,579	12.7
65 yr +	59	1,765	144	2,441	29,915	12.3

SOURCE: Health Care Financing Administration, Bureau of Data Management and Strategy: Data from the Program Management and Medical Information System, 1985.

Table 1-25

Discharge Rates for Medicare Functioning Kidney Graft Patients, by Days of Care Rates and Average Length of Stay: 1985

Number Age Group	Number of of Patients	Number of Inpatient Days	Discharges Inpatient Discharges	Days Per Per 1,000 Persons	Average 1,000 Persons	Length Stay
Total	17,926	97,316	11,551	644	5,429	8.4
Under 15 yr	613	2,863	364	594	4,670	7.9
15-24 yr	2,306	9,270	1,253	543	4,020	7.4
25-34 yr	5,163	26,149	3,170	614	5,065	8.2
35-44 yr	4,832	27,918	3,256	674	5,778	8.6
45-54 yr	3,239	19,470	2,187	675	6,011	8.9
55-64 yr	1,612	10,696	1,209	750	6,635	8.8
65 yr +	161	950	112	696	5,901	8.5

SOURCE: Health Care Financing Administration, Bureau of Data Management and Strategy: Data from the Program Management and Medical Information System, 1985.

were few patients, there was a direct relationship between inpatient use and age. Persons 55-64 years of age were hospitalized 38 percent more often than persons age 15-24 (750 discharges per 1,000 and 543 discharges per 1,000, respectively) and experienced 65 percent more inpatient days (6,635 days per 1,000 and 4,020 days per 1,000, respectively).

Persons Receiving a Transplant in a Year Prior to 1985, with a Kidney Graft Failure in 1985--

The final group of ESRD beneficiaries represents those persons who received a kidney transplant before 1985 and experienced a graft failure in 1985. There were 917 of these persons, representing 0.9 percent of the total ESRD Medicare beneficiary population. Table 1-26 presents the inpatient utilization rates for these persons. The table shows that the rejection of a transplant is associated with a high rate of hospitalization. These persons accounted for 2,301 hospitalizations and a total of 20,373 inpatient days. This utilization amounts to a discharge rate of 2,509 discharges per 1,000 beneficiaries, and a days-of-care rate of 22,217 per 1,000 beneficiaries. There is little relationship between age and utilization in this patient population with most age groups experiencing discharge rates of greater than 2,000 per 1,000 beneficiaries and days of care rates greater than 20,000 per 1,000 beneficiaries.

Transplant Recipient Hospitalization for Ancillary Problems

HCFA staff have also conducted an analysis of what are referred to as "ancillary" hospitalizations of transplant recipients. These are defined as all hospitalizations other than transplants. This is a necessary simplification

Table 1-26

Discharge Rates for Medicare Kidney Graft Failure Patients, by Days of Care Rates and Average Length of Stay: 1985

Number Age Group	Number of of Patients	Number of Inpatient Days	Discharges Inpatient Discharges	Days Per Per 1,000 Persons	Average 1,000 Persons	Length Stay
Total	917	20,373	2,301	2,509	22,217	8.9
Under 15 yr	38	708	81	2,132	18,632	8.7
15-24 yr	150	3,247	370	2,467	21,647	8.8
25-34 yr	250	5,714	673	2,692	22,856	8.5
35-44 yr	233	5,517	614	2,635	23,678	9.0
45-54 yr	171	3,420	384	2,246	20,000	8.9
55-64 yr	71	1,727	176	2,479	24,324	9.8
65 yr +	4	40	3	750	10,000	13.3

SOURCE: Health Care Financing Administration, Bureau of Data Management and Strategy: Data from the Program Management and Medical Information System, 1985.

because many hospitalizations are related to the transplant event, either before the actual transplant or afterward, such as rejection episodes. However, it is not possible to unequivocally identify which hospitalizations are transplant "related." For example, a patient might develop cancer that may or may not be associated with transplant immunosuppression. Therefore, the nontransplant stays of transplant patients are considered to be ancillary hospitalizations.

The data for the following analysis were extracted from the 1983 Medicare Provider Analysis and Review File (MEDPAR), which is a 20 percent sample of hospital stays for Medicare beneficiaries. This sample of stays includes procedure coding so it was possible for HCFA staff to determine average charges and length of stay for transplant and nontransplant stays. The 1983 MEDPAR contained a slight shortfall (about one percent) at the time of the analysis. Thus, the figures were adjusted upward to approximate costs for 100 percent stays. Hospital covered charges and covered days of care were estimated directly from the MEDPAR records.

Table 1-27 summarizes the results of this analysis. In 1983, Medicare end-stage renal disease (ESRD) patients had a total of 112,502 discharges. Of the total discharges, 53 percent were nonsurgical, 42 percent included a surgical procedure other than transplant, and the remaining five percent were for transplants.

Inpatient charges amount to almost $853 million for this population. Because of the relatively high cost of transplant stays, over one-fifth (22%) of all inpatient charges were for transplant stays. Overall, the average charge per stay for the ESRD population in 1983 was $7,584. The average transplant stay had a charge of $33,693, while the average ancillary (i.e.,

Table 1-27

Charges, Estimated Reimbursements, and Average Length of Stay for Transplant and Nontransplant Hospital Stays: 1983

Characteristic	All Stays	Transplant Stays	Nontransplant Stays All	 Non-surgical	 Surgical
Number of stays	112,502	5,616	106,886	59,158	47,728
Percent	100	5	95	53	42
Charges (in thousands)	$853,215	$189,220	$663,995	$221,648	$442,347
Percent	100	22	78	26	52
Charges	7,584	33,693	6,212	3,747	9,268
Estimated reimbursement (in thousands)	$553,737	$122,804	$430,933	$143,850	$287,083
Percent	100	22	78	26	52
Estimated reimbursement per stay	$4,922	$21,867	$4,032	$2,432	$6,015
Covered days	1,210,234	151,070	1,059,164	515,059	544,104
Percent	100	12	88	43	45
ALOS 1/	10.8	26.9	9.9	8.7	11.4

1/ Average length of stay

SOURCE: 1983 MEDPAR 20 percent sample of hospital stays, and Program Management and Medical Information System.

nontransplant) hospital stay had a charge of $6,212. Of the total ancillary stays, the average for surgical stays was $9,268.

Medicare reimbursements are not equal to hospital charges. Applying the national ratio of Medicare reimbursements to charges gives an estimate of the costs to Medicare for ESRD hospitalizations. In 1983 the cost to charges ratio was .649. That is, Medicare paid hospitals an average of 64.9 percent of charges. For all ESRD patients, estimated Medicare inpatient hospital payments were $554 million in 1983; $123 million for transplant, and $431 million for nontransplant (or ancillary) stays.

As noted earlier, nonsurgical stays comprised 53 percent of all stays, while the nontransplant surgical stays were 42 percent of the total. However, due to the higher costs of surgical stays, the nontransplant surgical stays accounted for 52 percent of all reimbursements. The estimated Medicare reimbursements per stay are $4,922 for all discharges, $21,867 for transplants, and $4,032 for all nontransplant stays. Among nontransplant stays, nonsurgical stays averaged $2,432 and surgical stays averaged $6,015.

Dialysis and Transplant Survival

HCFA staff have also analyzed dialysis and transplant survival. The results of this analysis are presented below. For dialysis patients, survival results were calculated based on the date of onset of renal failure. For transplant recipients, survival was keyed to the date of kidney transplant to three years posttransplant. The analysis covers the period from January 1, 1982, through January 31, 1985.

All Medicare beneficiaries with renal failure occurring on or after January 1, 1982 through December 31, 1985 were included in the analysis of dialysis survival. The transplant survival analysis included Medicare beneficiaries whose transplants occurred on or after January 1, 1982, through December 31, 1985. The total number of persons included in the computation of dialysis patient survival was 101,279. The total number of transplants included in the computation of transplant survival was 23,724.

Computation of survival rates for dialysis patients requires a date of renal onset and a date of death. Computation of graft and patient survival rates for transplant recipients requires the date of transplantation, date of graft failure, and date of death. Dates of death were taken from the Master Beneficiary Records which are maintained for all Medicare beneficiaries. The determination of renal failure onset was defined as the date of first dialysis and was taken from the patient medical evidence record (HCFA-2728), the outpatient dialysis record (HCFA-1483), or was estimated from the entitlement records. The date of transplant was taken from the transplant form (HCFA-2745) or from the inpatient hospital bill (HCFA-1453). The date of transplant failure was calculated based on a record of outpatient dialysis sessions or on a retransplant date.

Survival rates were calculated using a standard actuarial modified life-table analysis. For dialysis patients, survival was measured from date of renal failure onset until death with right censoring for transplantation or the end of the observation period (December 31, 1986). For transplants, patient survival was measured from date of transplantation until death with right censoring for the end of the observation period. Graft survival for transplants was measured from date of transplantation until graft failure date or date of death with right censoring for the end of the observation period.

Table 1-28 presents the results of the analysis of dialysis patient survival. At one year following renal failure onset, 78.2 percent of patients were still alive. At two years this had decreased to 62.5 percent and at three years, 50.1 percent. There were notable differences by age group. Persons less than 25 years of age (at the time of renal failure) had a 1-year survival of over 95 percent and a three-year survival rate of over 85 percent. The rate of survival decreased for each older age cohort. For those over 75 year of age, 1-year survival was only 57.7 percent and less than one-quarter (23.0%) could be expected to survive three years. At three years, females have a cumulative survival rate two percent greater than do males (51.1% and 49.1% respectively).

Among racial groups the highest survival is found in black persons (84.6% at one year and 59.8% at three years). Asian persons and American Indians have survival rates slightly below that of black persons. The lowest survival on dialysis is found among white persons with 1-year survival of 76.3 percent at one year and 47.2 percent at three years. The average age of white persons on dialysis is greater than for the other age groups. This explains part, but not all, of the racial differences in dialysis survival.

By reported cause of renal failure, the lowest survival rates are for those whose renal failure was attributed to diabetes (39.1% at three years) and hypertension (48.8% at three years). Persons whose renal failure is attributed to glomerulonephritis have a three-year survival rate of 63.0 percent and persons whose renal failure is attributed to polycystic kidney disease have a three-year survival rate of 74.1 percent. Tables 1-29 and 1-30 present patient survival rates for persons with cadaver transplants and living-related donor transplants, respectively. Among cadaver transplant recipients,

Table 1-28

Dialysis Patient Survival by Age, Sex, Race, and Primary Disease

Patient Characteristic	Number of Persons	Percent Surviving One Year	Two Years	Three Ye
All persons	101,279	78.2 (0.1)	62.5 (0.2)	50.1 (0.
Age				
Under 15 years	1,652	95.2 (0.6)	91.3 (1.0)	89.0 (1.
15-24 years	4,566	95.1 (0.4)	90.2 (0.6)	86.7 (0.
25-34 years	10,120	91.5 (0.3)	82.4 (0.5)	74.1 (0.
35-44 years	11,710	89.7 (0.3)	79.2 (0.4)	69.7 (0.
45-54 years	15,194	86.5 (0.3)	73.3 (0.4)	62.1 (0.
55-64 years	23,831	79.3 (0.3)	63.4 (0.3)	50.5 (0.
65-74 years	23,234	67.3 (0.3)	48.6 (0.3)	35.2 (0.
75 years or over	10,972	57.7 (0.4)	36.8 (0.5)	23.0 (0.
Sex				
Male	55,857	77.8 (0.2)	61.7 (0.2)	49.1 (0.
Female	45,422	78.6 (0.2)	63.4 (0.2)	51.1 (0.
Race				
White	63,656	76.3 (0.2)	59.9 (0.2)	47.2 (0.
Black	25,975	84.6 (0.2)	71.1 (0.3)	59.8 (0.
Asian	1,476	83.5 (1.0)	70.3 (1.3)	56.1 (1.
American Indian	966	83.2 (1.2)	68.0 (1.6)	54.6 (2.
Other/unknown	9,206	70.8 (0.5)	53.2 (0.6)	39.9 (0.
Primary disease				
Diabetes	25,743	74.3 (0.3)	53.9 (0.3)	39.1 (0.
Hypertension	24,348	76.4 (0.3)	61.0 (0.3)	48.8 (0.
Glomerulonephritis	22,382	85.4 (0.3)	73.4 (0.3)	63.0 (0.
Polycystic Kidney Disease	4,244	92.2 (0.4)	83.9 (0.6)	74.1 (0.
Other/unknown	24,562	75.1 (0.3)	59.8 (0.3)	47.6 (0.

NOTE: Numbers in parentheses represent the standard error of the estimate for each value.

SOURCE: Health Care Financing Administration, Bureau of Data Management and Strategy: Data from the Program Management and Medical Information System, 1982-1985.

Table 1-29

Cadaver Transplant Patient Survival by Age, Sex, Race, and Primary Disease: 1982-1985

Patient Characteristic	Number of Persons	Percent Surviving One Year	Two Years	Three Years
All persons	17,229	90.6 (0.2)	85.9 (0.3)	81.1 (0.4)
Age				
Under 15 years	657	95.1 (0.9)	92.9 (1.1)	89.1 (1.7)
15-24 years	2,106	95.2 (0.5)	92.4 (0.7)	89.0 (1.0)
25-34 years	4,435	93.0 (0.4)	89.2 (0.5)	84.7 (0.8)
35-44 years	4,764	90.7 (0.5)	85.5 (0.6)	80.3 (0.8)
45-54 years	3,577	87.2 (0.6)	81.6 (0.8)	76.7 (1.0)
55-64 years	1,562	83.4 (1.0)	75.9 (1.3)	68.0 (1.8)
65-74 years	120	77.5 (4.5)	73.3 (5.2)	67.9 (7.1)
75 years or over	8	--	--	--
Sex				
Male	10,957	90.5 (0.3)	85.8 (0.4)	80.2 (0.5)
Female	6,272	90.6 (0.4)	86.1 (0.5)	82.7 (0.7)
Race				
White	11,580	90.8 (0.3)	86.5 (0.4)	82.1 (0.5)
Black	3,762	91.8 (0.5)	87.2 (0.7)	82.3 (0.9)
Asian	288	89.0 (2.0)	84.7 (2.5)	82.3 (2.9)
American Indian	140	90.2 (2.7)	86.1 (3.5)	77.9 (5.5)
Other/unknown	1,459	86.2 (0.9)	80.1 (1.1)	74.3 (1.2)
Primary Disease				
Diabetes	2,705	85.6 (0.7)	77.3 (1.0)	68.7 (1.4)
Hypertension	2,185	90.2 (0.7)	85.3 (0.9)	79.6 (1.2)
Glomerulonephritis	5,358	93.4 (0.4)	90.3 (0.5)	86.7 (0.7)
Polycystic Kidney Disease	1,171	89.4 (1.0)	86.0 (1.2)	83.0 (1.5)
Other/unknown	5,822	90.6 (0.4)	85.8 (0.5)	81.4 (0.7)

NOTE: Numbers in parentheses represent the standard error of the estimate for each value.

SOURCE: Health Care Financing Administration, Bureau of Data Management and Strategy: Data from the Program Management and Medical Information System, 1982-1985.

Table 1-30

Living-Related Donor Transplant Patient Survival by Age, Sex, Race, and Primary Disease: 1982-85

Patient Characteristic	Number of Persons	Percent Surviving One Year	Percent Surviving Two Years	Percent Surviving Three Yea
All persons	6,495	95.8 (0.3)	93.7 (0.3)	91.1 (0.5
Age				
Under 15 years	657	97.4 (0.7)	96.1 (0.9)	93.9 (1.3
15-24 years	1,422	97.8 (0.4)	97.0 (0.5)	95.8 (0.7
25-34 years	2,150	96.9 (0.4)	95.1 (0.5)	92.4 (0.8
35-44 years	1,283	94.1 (0.7)	91.4 (0.9)	87.7 (1.2
45-54 years	740	92.5 (1.0)	88.2 (1.4)	85.5 (1.7
55-64 years	232	88.0 (2.3)	83.8 (2.8)	77.2 (3.6
65-74 years	11	--	--	--
75 years or over	0	--	--	--
Sex				
Male	3,957	96.1 (0.3)	94.0 (0.4)	91.0 (0.6
Female	2,538	95.2 (0.5)	93.3 (0.6)	91.2 (0.7
Race				
White	5,074	96.3 (0.3)	94.4 (0.4)	91.6 (0.5
Black	738	93.4 (1.0)	90.8 (1.2)	86.8 (1.7
Asian	94	94.9 (2.5)	93.3 (2.9)	93.3 (2.9
American Indian	70	91.6 (3.6)	91.6 (3.6)	91.6 (3.6
Other/unknown	519	94.5 (1.0)	92.0 (1.2)	90.3 (1.3
Primary Disease				
Diabetes	1,145	91.3 (0.9)	86.2 (1.2)	80.7 (1.6
Hypertension	496	95.3 (1.0)	92.7 (1.3)	89.0 (1.9
Glomerulonephritis	2,207	97.6 (0.3)	96.7 (0.4)	95.4 (0.6
Polycystic Kidney Disease	234	97.1 (1.2)	96.4 (1.4)	96.4 (1.4
Other/unknown	2,336	96.1 (0.4)	94.4 (0.5)	91.7 (0.8

NOTE: Numbers in parentheses represent the standard error of the estimate for each value.

SOURCE: Health Care Financing Administration, Bureau of Data Management and Strategy: Data from the Program Management and Medical Information System, 1982-1985.

1-, 2-, and 3-year patient survival rates are 90.6 percent, 85.9 percent, and 81.1 percent, respectively. Patient survival decreased with advancing age, with three-year survival rates of 89 percent for persons less than 25 years old, falling to 68 percent for persons ages 65-74. Females had three-year survival rates about two percent greater than males (82.7% and 80.2% respectively). White persons, black persons, and Asian persons all had three-year survival rates of about 82 percent. Patient survival was lower among American Indians at 77.9 percent. Persons whose renal failure was attributed to glomerulonephritis had the highest three-year survival rate at 86.7 percent and persons with diabetes had the lowest three-year survival rate at 68.7 percent.

Among living-related donor transplant recipients, 1-, 2-, and 3-year patient survival rates were 95.8 percent, 93.7 percent, and 91.1 percent, respectively. Three-year patient survival rates ranged from a high of 95.8 percent for persons 15-24 years of age, to 77.2 percent for persons 55-64 years of age. Males and females had comparable three-year survival rates of about 91 percent. Asian persons had the highest three-year survival rate of 93.3 percent, followed by white persons and American Indians (91.6%) and black persons (86.8%). By cause of renal failure, persons whose renal failure was attributed to either glomerulonephritis or polycystic kidney disease had three-year survival rates over 95 percent. Survival for persons with hypertension was 89.0 percent, and for persons with diabetes, survival was 80.7 percent.

Tables 1-31 and 1-32 present kidney graft survival rates for persons with cadaver transplants and living-related donor transplants, respectively. Among cadaver donor recipients, about two-thirds of the kidney grafts

Table 1-31

Cadaver Transplant Graft Survival in Patients by Age, Sex, Race, and Primary Disease: 1982-1985

Patient Characteristic	Number of Persons	Percent Surviving One Year	Percent Surviving Two Years	Percent Surviving Three Ye
All persons	17,229	66.2 (0.4)	58.5 (0.4)	52.1 (0.
Age				
Under 15 years	657	59.3 (2.0)	49.1 (2.3)	42.1 (2.
15-24 years	2,106	67.2 (1.1)	59.5 (1.2)	52.5 (1.
25-34 years	4,435	67.8 (0.7)	60.2 (0.8)	53.8 (1.
35-44 years	4,764	65.8 (0.7)	58.4 (0.8)	52.5 (1.
45-54 years	3,577	65.7 (0.9)	58.4 (1.0)	52.3 (1.
55-64 years	1,562	65.6 (1.3)	56.6 (1.5)	49.1 (1.
65-74 years	120	58.4 (5.3)	53.9 (5.8)	53.9 (5.
75 years or over	8	---	--	--
Sex				
Male	10,957	66.2 (0.5)	58.4 (0.5)	51.8 (0.
Female	6,272	66.1 (0.6)	58.6 (0.7)	52.6 (0.
Race				
White	11,580	67.5 (0.5)	60.5 (0.5)	54.3 (0.
Black	3,762	62.2 (0.9)	52.0 (1.0)	44.6 (1.
Asian	288	65.7 (3.0)	59.0 (3.3)	55.8 (3.
American Indian	140	69.9 (4.2)	57.2 (5.1)	41.3 (1.
Other/unknown	1,459	65.9 (1.3)	58.4 (1.3)	53.4 (1.
Primary Disease				
Diabetes	2,705	65.1 (1.0)	56.6 (1.2)	48.9 (1.
Hypertension	2,185	65.9 (1.1)	56.3 (1.3)	49.1 (1.
Glomerulonephritis	5,358	68.0 (0.7)	60.9 (0.8)	54.3 (0.
Polycystic Kidney Disease	1,171	66.5 (1.5)	60.3 (1.6)	56.8 (1.
Other/unknown	5,822	65.0 (0.7)	57.4 (0.7)	51.6 (0.

NOTE: Numbers in parentheses represent the standard error of the estimate for each value.

SOURCE: Health Care Financing Administration, Bureau of Data Management and Strategy: Data from the Program Management and Medical Information System, 1982-1985.

Table 1-32

Living-Related Donor Transplant Graft Survival of Patients by Age, Sex, Race, and Primary Disease: 1982-1985

Patient Characteristic	Number of Persons	Percent Surviving One Year	Percent Surviving Two Years	Percent Surviving Three Years
All persons	6,495	86.4 (0.5)	81.0 (0.6)	77.1 (0.7)
Age				
Under 15 years	657	82.3 (1.6)	75.3 (1.9)	70.1 (2.4)
15-24 years	1,422	88.9 (0.9)	82.6 (1.1)	79.4 (1.3)
25-34 years	2,150	88.2 (0.7)	83.5 (0.9)	79.0 (1.1)
35-44 years	1,283	84.4 (1.1)	79.8 (1.3)	77.2 (1.4)
45-54 years	740	85.3 (1.4)	78.7 (1.7)	75.2 (2.0)
55-64 years	232	80.0 (2.8)	77.2 (3.1)	71.5 (3.7)
65-74 years	11	--	--	--
75 years or over	0	--	--	--
Sex				
Male	3,957	86.4 (0.6)	80.4 (0.7)	76.1 (0.9)
Female	2,538	86.4 (0.7)	81.9 (0.9)	78.8 (1.0)
Race				
White	5,074	87.4 (0.5)	82.2 (0.6)	77.7 (0.8)
Black	738	77.3 (1.6)	68.7 (2.0)	64.1 (2.3)
Asian	94	90.5 (3.2)	85.5 (4.1)	85.5 (4.1)
American Indian	70	82.9 (4.8)	78.2 (5.5)	78.2 (5.5)
Other/unknown	519	89.2 (1.4)	84.8 (1.6)	83.4 (1.7)
Primary Disease				
Diabetes	1,145	83.0 (1.2)	76.5 (1.4)	70.7 (1.8)
Hypertension	496	86.3 (1.6)	76.8 (2.2)	72.5 (2.6)
Glomerulonephritis	2,207	87.1 (0.7)	81.8 (0.9)	78.3 (1.1)
Polycystic Kidney Disease	234	88.5 (2.2)	87.1 (2.4)	81.8 (3.4)
Other/unknown	2,336	87.1 (0.7)	82.6 (0.9)	79.5 (1.0)

NOTE: Numbers in parentheses represent the standard error of the estimate for each value.

SOURCE: Health Care Financing Administration, Bureau of Data Management and Strategy: Data from the Program Management and Medical Information System, 1982-1985.

survived, and at three years just over one-half (52.1%) were still functioning. There was little difference in graft survival across age and sex groups with almost all groups having three-year survival rates of about 50 percent. Asian and white cadaver transplant recipients had three-year graft survival rates of 55.8 percent and 54.3 percent, respectively. Lower graft survival rates were experienced by black recipients (44.6%) and American Indian recipients (41.3%). There were small differences in graft survival by primary disease category with persons with glomerulonephritis (54.3%) and polycystic kidney disease (56.8%) having higher survival rates than persons with hypertension (49.1%) and diabetes (48.9%).

Among persons receiving a transplant from a living-related donor, 1-, 2-, and 3-year graft survival rates were 86.4 percent, 81.0 percent, and 77.1 percent, respectively. As with cadaver transplant recipients, there were not great differences by age group. However, the youngest group (ages less than 15) and the oldest age group had the lowest survival rates. Females had a slightly higher survival rate (78.8%) than did males (76.1%). Differences by race group were quite high ranging from a high of 85.5 percent among Asian persons to a low of 64.1 percent among black persons. By primary disease category, three-year graft survival rates were highest for persons whose renal failure was attributed to polycystic kidney disease (81.3%) or glomerulonephritis (78.3%) and lowest for persons whose renal failure was attributed to either hypertension (72.5%) or diabetes (70.7%).

Providers of Renal Transplantation Services

Over the past several years there has been a steady increase in the number of hospitals in the United States providing renal transplantation services. As shown, Table 1-33, there were 157 Medicare-approved kidney transplant centers in 1981. Currently 210 renal transplant centers are members of the United Network for Organ Sharing (UNOS)--the National Organ Procurement and Transplantation Network. Therefore, over a seven-year period there has been a 33.8 percent increase in the number of kidney transplant centers.

Data on the volume of kidney transplants by center is interesting. In 1987, 35 percent of the renal transplant centers in the United States performed between 0 and 24 transplants (see Table 1-34). Only three centers performed 200 or more procedures, while 33.5 percent of the centers performed between 25 and 49 transplants.

Table 1-35 is a listing of the 20 highest volume kidney transplant centers in the United States in 1987. While there is some year-to-year variation in the centers that appear on the list, there is remarkable consistency in the ten top centers.

Despite the fact that many kidney transplant centers perform relatively few procedures, there is no attempt being made by the Health Care Financing Administration or the United Network for Organ Sharing to regionalize transplant programs. Both organizations do, however, have very explicit conditions of participation. While HCFA, on paper, places emphasis on minimum utilization rates (volume requirements), UNOS has much more specific staffing and facility requirements. Neither organization, however, has effectively denied participation to any hospital seeking what might be referred to as "certification." This, of course, is not surprising, given the spirit of competition, as opposed to regulation, that permeates much of the health care delivery system today.

Table 1-33

Number of Kidney Transplant Programs in the United States, by Year

Year	Number of Programs
1981	157
1982	159
1983	159
1984	170
1985	176
1986	185
1987	199
1988	210

Table 1-34

Number of Kidney Transplants Performed by Center, 1987

Number of Transplants	Number of Centers	Percent
0	6	3.0
0-10	30	15.0
11-24	35	17.5
25-49	67	33.5
50-74	30	15.0
75-99	13	6.5
100-124	7	3.5
125-149	4	2.0
150-174	3	1.5
175-199	2	1.0
200-225	3	1.5

Table 1-35

The Top Twenty Kidney Transplant Programs in the United States, 1987

	Center	Total Number of Transplants 1987	1986
1.	University of Alabama, Birmingham	218	223
2.	University of California, San Francisco	207	245
3.	St. Vincent Medical Center, Los Angeles	203	167
4.	Presbyterian-University Hospital, Pittsburgh	193	270
5.	University of Wisconsin, Madison	190	206
6.	University of Minnesota, Minneapolis	160	171
7.	Pacific Medical Center, San Francisco	158	211
8.	Ohio State University, Columbus	153	125
9.	Methodist Medical of Dallas, Dallas	146	175
10.	Downstate Medical Center, Brooklyn	139	125
11.	University of Oregon, Portland	135	122
12.	Shands Teaching Hospital, Gainesville	133	101
13.	Washington Hospital Center, Washington, DC	121	112
14.	Vanderbilt University, Nashville	119	116
15.	Emory University, Atlanta	117	130
16.	Hermann Hospital, Houston	114	101
17.	Tampa General Hospital, Tampa	111	94
18.	Good Samaritan Medical Center, Phoenix	105	116
19.	University of Pennsylvania, Philadelphia	102	122
20.	University of Michigan, Ann Arbor	95	107
	UCLA, Los Angeles	95	85

Discussion

This chapter has provided a comprehensive overview of various clinical and social aspects of the treatment of end-stage renal disease, with emphasis on those features that are more relevant to kidney transplantation. With the advent of cyclosporine, it is apparent that much progress has been made in renal transplantation. In many respects, cyclosporine made kidney transplantation a clinical reality of sufficient proportion that it realistically challenged kidney dialysis. There is little doubt that, as observed by Eggers (1988:223), "...renal transplantation is causing a convergence of the best clinical and economic outcomes for patients with end-stage renal disease." Nonetheless, because of a growing ESRD patient population, many members of which are not eligible for kidney transplantation and, in light of a severe shortage of donor organs, program expenditures continue to increase at a disconcerting rate. This has led many policymakers to question the long-term prognosis of the treatment of renal failure in the United States. There are those who feel that fewer patients should be treated in an effort to contain program expenditures. This, of course, is the ESRD health policy dilemma alluded to previously.

The policy "history" of kidney transplantation has been very favorable, certainly since 1983, when public pleas for pediatric liver donors riveted attention on organ transplantation more generally. It was also during this period that the relatively high cost of cyclosporine, in comparison with conventional immunosuppressive therapy, brought additional legislative efforts to minimize the stark economic reality that many transplant recipients faced--they could not afford the very drugs that assured the long-term functioning of their kidney. These efforts proved successful and, with the passage of the Medicare Catastrophic Coverage Act in June, 1988, the long-term financial prognosis for the payment of immunosuppressive drugs appears reasonably assured. Yet, in other respects, it is apparent that other financial woes may well befall the ESRD Program. With recombinant human erythropoietin projected to cost as much as $9,000 per patient year, it is likely that further economic crisis is inevitable, perhaps renewing plans to reduce program expenditures by treating fewer patients, reserving treatment for those who have the most favorable clinical prognosis.

The ESRD Program statistics reviewed here clearly direct attention to the probable order and magnitude of the problems the future will hold. Summarized succinctly, we can say there is more disease, more treatment, moderate utilization among younger patients, improved survival for selected patients, all, however, at an increasing cost to the Medicare program. Moreover, since large numbers of patients are not rehabilitated sufficiently well to return to "substantial gainful activity," as defined by the Social Security Administration, these patients ultimately become the recipients of income support payments through the Social Security Disability Benefits Program or the Supplemental Security Income Program. For example, during the National Kidney Dialysis and Kidney Transplantation Study (NKDKTS), we learned that nearly half of all transplant recipients were receiving Social Security benefits (disability or retirement) or Supplemental Security Income, even though the average age of such patients was 37 years (see Evans et al., 1987). Of the in-center hemodialysis patients in the same study, over 76 percent were receiving income support from federal programs, and, overall, over 67 percent of ESRD patients were receiving income support. Despite those sources of support, over 30 percent of in-center hemodialysis patients, and over 16 percent of transplant recipients, have household incomes below the poverty line (Evans et al., 1987:1-193).

Finally, while there are no obvious problems associated with the provision of renal transplant services, the proliferation of such services, and concerns related to costs and outcomes, are likely to be central issues over the next several years. There has been a marked increase in the number of renal transplant centers, and there are wide variations in overall results, although costs are somewhat constrained by Medicare's prospective payment system. The public release of center-specific outcome data will certainly be a major item on the agenda. Providers are hesitant to release such data, citing the negative fallout from HCFA's release of hospital-specific mortality data (Luft and Hunt, 1986:2780; Ginsburg and Hammons, 1988:108; Jencks et al., 1988:3611; Daley et al., 1988:3617; Kahn et al., 1988:3625). Nevertheless, public sentiment favoring the release of such data may well hold sway. All of this, however, is unlikely to markedly affect the number and distribution of transplant programs. Regionalization clearly is not a concept that will gain much favor, although some private insurers have implemented procedures for designating transplant centers (International Medical Tribune Syndicate, 1988:22; Ascher and Evans, 1987:2405; Evans, 1987:966; Renlund et al., 1987:873; National News, 1988:12). Through designation, insurers essentially limit reimbursement to selected providers based on favorable outcomes and an a priori negotiated price.

To be sure, the future of the treatment of end-stage renal disease will be uncertain. The primary focus of this report is on the costs and benefits of various approaches to transplant immunosuppression, both key ingredients in assuring the continued success of kidney transplantation as the optimal form of therapy for ESRD. Most important, this report brings together a very diverse set of clinical and social issues that must be analyzed in a manner that will facilitate the formulation of public health policy.

CHAPTER 2

DATA COLLECTION METHODOLOGY

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CHAPTER 2 DATA COLLECTION METHODOLOGY

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Introduction

Data for the study were collected on a total of 396 renal transplant recipients who received a transplant at one of five participating transplant centers. The transplant centers that were selected to participate in the study include: (1) University of California, San Francisco; (2) Ohio State University; (3) University of Pittsburgh; (4) University of Texas, Houston; and (5) University of Wisconsin. Data were obtained from two major sources. Medical background information, information regarding the transplant procedure and immunosuppressive treatment protocol, information concerning complications and other outcome variables, as well as transplant related costs were extracted from the patients' medical and hospital billing records maintained by the transplant centers. In addition, patient outcome data were obtained through a series of patient questionnaires.

Four data collection forms were developed for use in the study. They include:

- A Baseline Medical Records Data Abstraction Form--completed by a data collector at the transplant center as soon as possible after discharge from the hospital following the transplant surgery.
- A Follow-up Medical Records Information Form--completed by a data collector at the transplant center at 3-month intervals following the transplant surgery.
- A Patient Baseline Questionnaire--completed by the patient three months posttransplant.
- A Follow-up Patient Questionnaire--completed by the patient at 3-month intervals beginning six months posttransplant.

The various data collection forms as well as the data collection protocols are described in greater detail later in this chapter.

The data were gathered prospectively over an 18-month data collection period. Patient intake began November 1, 1985 and continued through

October 31, 1986. Patients who received a transplant at one of the five participating transplant centers and who satisfied the patient eligibility criteria were asked to participate in the study. Data collection continued for a period of 6 to 18 months, depending upon when the recipient received his or her transplant.

Selection of Participating Transplant Centers

Prior to data collection, a subcontract was signed with each participating transplant center for the collection of patient medical records and hospital billing data. Each transplant center was responsible for hiring a data collector for that center. The data collector at each transplant center was responsible for (1) identifying patients who met the patient eligibility criteria for inclusion in the study, (2) obtaining patient consent to participate in the study, and (3) completing Baseline and Follow-up Medical Records Information Forms for all patients included in the study. The data collectors were trained by Battelle staff during a two-day training session held in Seattle on October 22-23, 1985.

The five participating transplant centers were selected with the expectation that during the one-year patient intake period each center would recruit between 60 and 100 kidney transplant patients for the study. Patient intake continued at each center during the entire one-year period or until approximately 100 patients from the center had been recruited for the study. Patients at the University of Pittsburgh were recruited during a nine month patient intake period. At the other four transplant centers patients were recruited over a period of 12 months. The number of patients recruited for the study at each of the five participating transplant centers was as follows:

University of California, San Francisco	108
Ohio State University	59
University of Pittsburgh	104
University of Texas, Houston	36
University of Wisconsin	89

It should be recognized that these five participating centers represent a purposive, rather than a random, sample of renal transplant centers in the United States. Thus, there are limitations on the extent to which the results of this study can be generalized to the renal transplant patient population as a whole.

Identification of Eligible Patients

Patients who received a kidney tranplant at one of the five participating transplant centers between November 1, 1985 and October 31, 1986 and who satisfied the patient selection criteria were asked to participate in the study. A patient was considered eligible for the study if:

- The patient received a graft from a cadaveric donor.
- The patient had not received a previous transplant.
- The patient was 18 years of age or older at the time of transplant.
- The patient was eligible for Medicare benefits.
- Postoperative follow-up care was coordinated by the transplant center.

All patients who satisfied the above criteria were asked to participate in the study. Those patients who agreed to participate were asked to sign two consent forms. The first, the Authorization for Review of Medical Records and Hospital Billing Information, provided permission for the abstraction of information from the patient's hospital and medical records (see Appendix A). If the patient signed this consent form, only data relevant to the kidney transplant and the treatment of the patient's kidney disease were abstracted. The second consent form--the General Consent Form--indicated the patient's willingness to complete a series of patient questionnaires (see Appendix B). Permission for the review of patients' medical and hospital records was considered essential to the study. If the patient refused permission for the abstraction of medical records data, the patient was excluded from the study. If, however, a patient provided his or her permission for the review of medical and hospital records but refused to participate in the Patient Surveys, the patient was not excluded from the study.

It should also be noted that a small number of patients were excluded from the study for medical or social reasons. In providing consent for participation in the study, it was essential that the patient be capable of understanding the nature of the study and the consequences of his or her participation. Moreover, the ability to understand the English language was necessary in order to complete the Baseline and Follow-up Patient Questionnaires. Therefore, if for medical or social reasons (i.e., mental retardation, blindness, psychological disorders, illiteracy, language difficulties) a patient was unable to provide informed consent, the patient was excluded from the study. Such exclusions were made in only a small number of cases.

After obtaining patient consent, the data collector at the center assigned each patient a unique study identification number and completed a General Information Form for each participating transplant recipient. The patient identification number was used to link the various patient questionnaire and medical and hospital records data files obtained during the data collection period. The General Information Form was used to record information including the patient's name, address, telephone number, study identification number and transplant date. This information was then sent to Battelle for use in administering the Baseline and Follow-up Patient Questionnaires.

Patient Exclusion and Withdrawal

As noted earlier, prior to data collection some transplant recipients were excluded from the study for one of several reasons. These include:

- Patient did not meet eligibility criteria.
- Patient refused to participate in the study.
- Patient was unable to participate for medical or social reasons.

In addition, some patients were not included in the study because they died or experienced a graft failure before patient consent could be obtained. If a patient was excluded from the study for one of the above reasons, an Exit Form was completed indicating the reason for patient exclusion.[1]

The numbers of patients who were excluded from the study by center, as well as by reason for exclusion, are shown in Table 2-1. Of the 780 patients who received transplants at the five participating transplant centers during the patient intake period, a total of 293 were initially excluded from the study because they did not meet the patient elibility criteria (they were too young, received a graft from a living-related donor, had received a previous transplant, were not Medicare eligible, etc.). In addition, three patients died and 19 patients experienced graft failures before consent could be obtained.

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[1] Although these patients were excluded from both the patient and medical records portions of the study, patients who died or experienced a graft failure before permission could be obtained, patients who were excluded for medical or social reasons, and patients who refused to participate in the study were included in the analysis of graft and patient survival.

Table 2-1

Number of Patients Excluded from the Study by Center and Reason for Exclusion

	University of California	Ohio State University	University of Pittsburgh	University of Texas	University of Wisconsin	TOTAL
Total Transplants Performed During Intake Period	171	143	232	103	131	780
Patient Failed to Meet Eligibility Criteria	59	58	90	47	39	293
Patient Died Prior to Obtaining Consent	0	1	2	0	0	3
Patient Experienced Graft Failure Prior to Consent	1	2	9	6	1	19
Patient Excluded for Medical/Social Reasons	0	12	19	12	1	44
Patient Refused to Participate in Study	3	11	8	2	1	25
Total Number of Patients Who Agreed to Participate in Study	108	59	104	36	89	396

Of the remaining patients, a total of 44 patients were excluded for various other medical or social reasons (i.e., difficulty understanding the English language, blindness, illiteracy, learning disabilities, and psychological disorders). Only 25 patients initially refused to participate in the study.

In addition to the initial exclusion of patients who were unable or unwilling to participate in the study, some patients were withdrawn from the study during the follow-up data collection period. Reasons for patient withdrawal include:

- Patient death.
- Graft failure--the patient experienced a graft failure at some time during the follow-up period and returned to dialysis or received a second transplant.
- Patient relocation--the patient moved during the follow-up period and follow-up care was no longer coordinated by the transplant center.
- Patient preference--the patient requested that he or she be withdrawn from the patient questionnaire portion of the study, the medical records portion of the study, or from the entire study at some time during the follow-up period.

The numbers of patients who were withdrawn from the study during the follow-up data collection period by transplant center, as well as by reason for withdrawal, are shown in Table 2-2. Of the 396 patients who initially agreed to participate in the study, a total of 65 were withdrawn from both the medical records and patient survey portions of the study at some time during the follow-up data collection period (8 because of death, 52 because of graft failure, and 5 because of relocation). Data were being collected from the medical records of 331 patients at the end of the follow-up period.

As noted earlier, participation in the medical records portion of the study was considered essential to the study. However, patients who gave their permission for the abstraction of medical records data but refused to participate in the patient surveys were included in the study. As can be seen in Table 2-2, 384 of the 396 patients initially agreed to participate in the patient portion of the study. During the follow-up period some of these patients were withdrawn from the study because of death, graft failure or relocation. In addition, 61 patients were withdrawn from this portion of the study by patient preference at some time during the follow-up period. In some cases these patients actually expressed a desire to withdraw from the study. In other cases they were withdrawn from the patient portion of the study after they failed to return baseline or follow-up questionnaires. A total of 258 patients were still active participants in the patient survey portion of the study at the end of the follow-up period.

Data Collection Instruments and Protocols

Baseline Medical Records Data Abstraction Form

The Baseline Medical Records Data Abstraction Form (see Appendix C) was used to obtain information concerning the patient's medical history, the transplant procedure, donor characteristics, and transplant costs. Examples of specific information requested with this form include:

- Personal background information (i.e., age, sex, race, height, weight).
- Information concerning the patient's renal disease and treatment history.
- Comorbid conditions at time of transplant.
- Patient disability prior to transplant (as evaluated by transplant center staff familiar with the transplant recipient).
- Details of the transplant procedure (i.e., pre-transplant blood transfusions, specific procedures performed, revascularization time, post-transplant dialysis, initial immunosuppressants received).

Table 2-2
Number of Patients Withdrawn from Medical Records and Patient Portions of the Study by Center and Reason for Withdrawal

	Medical Records Portion of Study					Patient Portion of Study					
Transplant Center	Number Initially Agreed to Participate	Patient Died During Follow-up Period	Graft Failed During Follow-up Period	Patient Moved During Follow-up Period	Number Participating For Entire Period	Number Initially Agreed to Participate	Patient Died During Follow-up Period	Graft Failed During Follow-up Period	Patient Moved During Follow-up Period	Patient Withdrew by Patient Preference*	Number Participating For Entire Period
University of California, San Francisco	108	4	14	1	89	104	4	14	1	19	66
Ohio State University	59	0	0	0	59	58	0	0	0	9	49
University of Pittsburgh	104	2	26	3	73	104	2	26	3	18	55
University of Texas Houston	36	2	5	1	28	36	2	5	1	3	25
University of Wisconsin	89	0	7	0	82	82	0	7	0	12	63
Total	396	8	52	5	331	384	8	52	5	61	258

*Patients were withdrawn either because they expressed a desire to be withdrawn from the study or they were withdrawn by the survey specialist for failure to return baseline or follow-up questionnaires.

- Donor characteristics (i.e., age sex, race, comorbid conditions, drugs administered in 24 hours prior to organ removal, urine output prior to organ removal).
- Details of organ removal (other organs removed for transplantation, warm ischemia time, cold time, total pulsatile perfusion time).
- Itemized costs of the transplant surgery.
- Sources of payment for immunosuppressive drugs.

In order to complete the Baseline Medical Records Data Abstraction Form it was necessary for the data collector to consult several sources. These include the patient's medical records maintained by the transplant center, physician's surgery notes, and hospital billing records. In addition, it was often necessary to contact organ procurement programs to obtain information regarding organ donor characteristics and the details of organ removal.

As soon as possible after the transplant operation, the data collector began completing the Baseline Medical Records Data Abstraction Form. Much of the necessary information (i.e., information on the patient's medical history, the transplant procedure, and donor characteristics) was available before the patient was discharged from the hospital. However, because the form also requested information on the cost of the transplant procedure, it was not possible to complete the form until after the patient was discharged from the hospital. Completed data collection forms were then sent to Battelle for data entry and analysis.

Follow-up Medical Records Information Forms

Follow-up Medical Records Information Forms (see Appendix D) were used to record information on the patient's immunosuppressive protocol, laboratory and other test data, complications, and hospitalizations at three-month intervals throughout the follow-up data collection period. More specifically, the form requested the following information:

- Maintenance doses of various immunosuppressive drugs being administered at the beginning of the follow-up period (cyclosporine, azathioprine, steroids).
- Maintenance doses of various immunosuppressive drugs being administered at the end of the follow-up period (cyclosporine, azathioprine, steroids).
- Doses of specific drugs used to treat episodes of rejection during the follow-up period (steroids, ALG/ATG, monoclonal antibodies).
- Number of laboratory and other tests performed during the follow-up period (EKGs, chest x-rays, pelvic x-rays, I.V.P.s, renograms, kidney needle biopsies).
- Serum creatinine during the follow-up period (highest, lowest, and most recent).
- Number of episodes of renal dysfunction during the follow-up period and how the episodes were treated (decreased cyclosporine, increased steroids, ATG, monoclonal antibodies).
- Number of episodes of nephrotoxicity.
- Adverse reactions to cyclosporine (if patient was receiving cyclosporine during the follow-up period).
- Complications treated during the follow-up period.
- Number of times hospitalized during the follow-up period.
- Itemized costs of each hospital stay during the period.
- Date of graft failure and primary cause of transplant failure (if the recipient experienced a graft failure during the follow-up period).
- Date of death and primary cause of death (if the recipient died during the follow-up period).

The first Follow-up Medical Records Information Form covered the period from hospital discharge following transplant surgery until three months posttransplant. All other follow-up periods were of a three-month duration, unless the patient was withdrawn from the study during the follow-up period (for example, if the recipient died or experienced a graft failure). There was considerable variation in the number of Follow-up Medical Records

Information Forms completed for transplant recipients. If a patient received his or her transplant during the second month of the intake period, five follow-up forms were completed (at 3, 6, 9, 12, and 15 months posttransplant). If, however, the patient received a transplant in the 12th month of data collection, only 2 follow-up forms were completed (those at three and six months posttransplant). For those patients who experienced a graft failure before discharge from the hospital following transplant surgery, baseline data were collected but no follow-up data were obtained.

As soon as possible after the end of a follow-up period, the data collector at the transplant center completed the Follow-up Medical Records Information Form. As was the case with the Baseline Medical Records Data Abstraction Form, it was often necessary for the data collector to consult several sources to obtain the information requested on the Follow-up Medical Records Information Form. These sources include the patient's medical record and, if the patient was hospitalized during the follow-up period, hospital billing information. Completed Follow-up Medical Records Information Forms were then sent to Battelle for data entry and analysis.

Baseline Patient Questionnaires

The purpose of the Baseline Patient Questionnaire (see Appendix E) was to obtain information on the patient's health, family and social life, medical costs, overall quality of life, and experience with rehabilitation and social service agencies following his or her kidney transplant. In addition to personal background characteristics, the questions focused on the following general areas:

- The recipients's feeling of well-being and satisfaction with life in general.
- Limitations of daily activities--both current limitations and limitations one year prior to transplantation.
- Current employment status and employment status prior to transplantation.
- Health status--perceived health status, hospitalizations in the year prior to transplantation, disability days since transplantation.
- Frequency of specific symptoms before and since transplantation.
- Lifestyle--information regarding diet and exercise.
- Personal adjustment to the kidney transplant.
- Experience with various government programs and rehabilitation services.
- Hospitalizations, physician visits, x-rays and laboratory tests performed, and drugs prescribed since the transplant surgery.
- Sources of payment for immunosuppressive drugs.
- Current financial situation.
- Nottingham Health Profile and the Sickness Impact Profile--two standardized measures of health status.

The Baseline Patient Questionnaire was administered three months after the patient's transplant surgery utilizing a telephone-assisted mail survey. The Baseline Questionnaire was administered three months after surgery to allow sufficient time for the patient to recover from the surgery and to resume a normal lifestyle. Not all patients were sent Baseline Patient Questionnaires. Excluded from the survey were those who did not consent to this portion of the study, as well as those who were withdrawn from the study (because of death or graft failure) during the first three months posttransplant.

At the time of initial contact with the patient during the patient's hospitalization, the data collector obtained the patient's consent to participate in the study. If the patient agreed to complete the series of patient questionnaires, the data collector recorded the patient's name, current address, and telephone number on a General Information Form. This General Information Form was then sent to Battelle for use in administering the Baseline and Follow-up Patient Questionnaires.

Three months after the patient's transplant date (if the patient had agreed to participate in the patient survey portion of the study and had not been withdrawn from the study for any reason), the patient was sent a packet of survey materials. The packet contained the Baseline Patient Questionnaire (containing the patient's study identification number), a postage-paid return envelope, and a cover letter containing instructions for completing and returning the questionnaire. Patients were told to expect a telephone call from a survey specialist from Battelle approximately one week after receiving the survey materials. Patients were also given the name and telephone number of persons to contact if they had any questions or concerns.

Approximately ten days after the Baseline Patient Questionnaire was mailed, the survey specialist attempted to contact the transplant recipient. The purpose of this call was to confirm that the recipient had received the questionnaire and to answer any questions that the patient might have had regarding completion of the questionnaire. If the questionnaire was not received, the survey specialist confirmed the patient's current mailing address and a second questionnaire was sent. On a few occasions questionnaires were returned by the Post Office as undeliverable. In such cases the transplant center was contacted in an attempt to obtain a correct mailing address, and another attempt was made to send the Baseline Patient Questionnaire.

If after several weeks a completed questionnaire had not been received, additional telephone calls were made to answer questions and to encourage the patient to complete and return the questionnaire. If after receiving the questionnaire, the transplant recipient decided that he or she did not want to complete the patient questionnaires, the recipient was withdrawn from the patient survey portion of the study. All telephone contact with the patient was recorded on a Contact Summary Sheet.

Follow-up Patient Questionnaires

A series of follow-up patient questionnaires (see Appendix F) was utilized to assess the patient's health, family and social life, overall quality of life, and experience with rehabilitation and social services at three-month intervals, beginning six months after surgery. The form was also used to document hospitalizations, physicians visits, x-rays and diagnostic tests performed, and drugs prescribed during the three-month follow-up period. The questionnaire was similar to the Baseline Patient Questionnaire that was administered three months posttransplant. This was done to allow a comparison of the changes in variables such as health status or quality of life over time. The Follow-up Patient Questionnaire focused on the following general topics:

- The recipient's feeling of well-being and satisfaction with life in general.
- Limitations of daily activities.
- Current employment status.
- Health status--perceived health status, disability days during the three-month follow-up period.
- Frequency of specific symptoms during the three-month follow-up period.

- Lifestyle--information regarding diet and exercise.
- Personal adjustment to the kidney transplant.
- Experience with various government programs and rehabilitation services.
- Hospitalizations, physician visits, x-rays and laboratory tests performed, and drugs prescribed during the 3-month follow-up period.
- Sources of payment for immunosuppressive drugs.
- Nottingham Health Profile and/or the Sickness Impact Profile--two standardized measures of health status (the Nottingham Health Profile was administered with the 6, 12, and 15-month follow-up surveys and the Sickness Impact Profile was administered with the 9- and 12-month follow-up surveys).

The first Follow-up Patient Questionnaire was administered six months posttransplant (three months after the Baseline Patient Questionnaire was administered). Additional follow-up surveys were then conducted at three-month intervals for the remainder of the follow-up data collection period, unless the patient was withdrawn from the study during the follow-up period. As was true for the Follow-up Medical Records Forms, there was considerable variation in the number of Follow-up Patient Questionnaires completed by transplant recipients. If a patient received his or her transplant during the second month of the intake period, four follow-up forms were completed (at 6, 9, 12, and 15 months posttransplant). If, however, the patient received a transplant during the 12th month of data collection, only one follow-up form was completed (at six months posttransplant). Of course, not all patients were sent Follow-up Patient Questionnaires. Excluded from the survey were those who did not consent to this portion of the study, as well as those who were withdrawn from the study (because of death, graft failure, relocation, or patient preference) during the follow-up period.

Procedures for administering the Follow-up Patient Questionnaires were similar to those used in administering the Baseline Questionnaires. Six months following transplant surgery, participating transplant recipients were sent a packet of survey materials. The packet contained the Follow-up Patient Questionnaire (containing the patient's study identification number), a postage-paid return envelope, and a cover letter containing instructions for completing and returning the questionnaire. Patients were told to expect a telephone call from a survey specialist from Battelle approximately one week after receiving the survey materials. Patients were also given the name and telephone number of persons to contact if they had any questions or concerns.

Approximately ten days after the Follow-up Patient Questionnaire was mailed, the survey specialist attempted to contact the transplant recipient. The purpose of this call was to confirm that the recipient had received the questionnaire and to answer any questions that the patient might have had regarding completion of the questionnaire. If after several weeks a completed questionnaire had not been received, additional telephone calls were made to answer questions and to encourage the patient to complete and return the questionnaire. If after receiving the questionnaire, the transplant recipient decided that he or she did not want to complete the patient questionnaires, the recipient was withdrawn from the patient survey portion of the study.

These same procedures were repeated at three month intervals--at 9, 12, and 15 months posttransplant--for the remainder of the follow-up period. The only difference in the survey administration procedures was that after the first Follow-up Patient Questionnaire, recipients were no longer routinely called to confirm that they had received the survey materials and to answer questions. However, if after several weeks a completed questionnaire had not been received, follow-up telephone calls were made to encourage the patient to complete and return the questionnaire.

Consent and Confidentiality Procedures

Shortly after the transplant surgery, a data collector at the transplant center asked each eligible patient for his or her permission to participate in the study. As described earlier, those who agreed to participate were asked to sign two consent forms--one providing permission for the abstraction of information from the patient's medical and hospital billing records, and another indicating his or her willingness to complete a series of patient questionnaires. Respondents were fully informed ot the nature and purposes of the study and the uses that were to be made of the data. The consent forms provided Battelle with a written acknowledgement from each individual indicating that he or she was informed of:

- The objectives of the study.
- The procedures to be followed.
- Measures to be taken to ensure the information they provide is kept confidential.
- Possible discomforts or risks associated with their participation.
- Where to direct their inquiries concerning the study.
- The voluntary nature of their participation, their freedom to refuse any information, and their right to discontinue participation in the study at any time.

While they were signed by the participant, the consent forms did not contain the recipient's identification number. The various data collection forms were identified only with the recipient's identification number. They did not contain the recipient's name, address, or other information which could be used to directly identify individuals or to link their identification numbers with their names.

When returned, the completed data collection forms were filed separately from the consent forms. Except when necessary to match individual information, the lists of transplant recipients and their corresponding identification numbers were kept separately from all data files. The resulting computer data files identify participants only by identification number. Access to all identifying information was available only to authorized personnel. These procedures were used to protect the anonymity of transplant recipient's questionnaire responses and medical and hospital billing information.

Number of Data Collection Forms Completed

The numbers of Baseline and Follow-up Medical Records forms completed by transplant center and type of form are presented in Table 2-3. Baseline Medical Records Data Abstraction Forms were completed for all 396 kidney transplant patients who were included in the study. However, the number of Follow-up Medical Records Information Forms completed decreases with time for the various follow-up periods. This is true for two reasons. First, patients were withdrawn from the study because of death, graft failure, or relocation during the follow-up data collection period. For example, 18 patients died or experienced a graft failure before being discharged from the hospital following transplant surgery. No three-month Follow-up Medical Records Information Forms were expected for these patients. Second, fewer Follow-up Medical Records Information Forms were completed at 9, 12, and 15 months posttransplant because patients who were transplanted in the later months of the patient intake period were followed for a shorter period of time. As can be seen in Table 2-3, a total of 371 3-month follow-up forms, 352 6-month follow-up forms, 262 9-month follow-up forms, 151 12-month follow-up forms, and 87 15-month follow-up forms were received.

The numbers of Baseline and Follow-up Patient Questionnaires received by transplant center and type of questionnaire are presented in Table 2-4. As was true for the Follow-up Medical Information Records Forms, the number of Baseline and Follow-up Patient Questionnaires completed decreases with time during the follow-up data collection period. In addition to the two reasons cited above for the decrease in the number of completed Medical Records forms, two additional reasons contributed to the decrease in the number of completed patient questionnaires. In the case of the patient questionnaires, not all patients initially consented to participate in the patient survey portion of the study. Moreover, patients were withdrawn from the patient survey portion of the study during the follow-up data collection period by patient preference (or in some cases the patient was withdrawn from the patient survey portion of the study by the survey specialist if after repeated attempts, the patient failed to return completed questionnaires). In computing the response rates presented in Table 2-4, the following assumption were made:

- A Baseline Questionnaire was expected from all patients who initially agreed to participate in the patient portion of the study and who had not been withdrawn from the study because of death, graft failure, or relocation during the first 3 months posttransplant.

Table 2-3

Number of Baseline and Follow-up Medical Records Forms Completed

Transplant Center	Baseline Forms Number Exp.	Baseline Forms Number Rec.	Baseline Forms Percent Rec.	3 Month Follow-up Forms Number Exp.	3 Month Follow-up Forms Number Rec.	3 Month Follow-up Forms Percent Rec.	6 Month Follow-up Forms Number Exp.	6 Month Follow-up Forms Number Rec.	6 Month Follow-up Forms Percent Rec.	9 Month Follow-up Forms Number Exp.	9 Month Follow-up Forms Number Rec.	9 Month Follow-up Forms Percent Rec.	12-Month Follow-up Forms Number Exp.	12-Month Follow-up Forms Number Exp.	12-Month Follow-up Forms Percent Rec.	15-Month Follow-up Forms Number Exp.	15-Month Follow-up Forms Number Rec.	15-Month Follow-up Forms Percent Rec.
University of California, San Francisco	108	108	100.0	103	103	100.0	95	95	100.0	62	62	100.0	38	38	100.0	21	21	100.0
Ohio State University	59	59	100.0	59	55	93.2	59	59	100.0	40	40	100.0	22	22	100.0	17	17	100.0
University of Pittsburgh	104	104	100.0	97	97	100.0	85	85	100.0	80	80	100.0	54	54	100.0	29	29	100.0
University of Texas Houston	36	36	100.0	31	28	90.3	32	30	93.8	19	17	89.5	9	9	100.0	4	3	75.0
University of Wisconsin	89	89	100.0	88	88	100.0	85	85	100.0	63	63	100.0	28	28	100.0	17	17	100.0
Total	396	396	100.0	378	371	98.1	356	352	98.8	264	262	99.2	151	151	100.0	88	87	98.9

Table 2-4

Number of Baseline and Follow-up Patient Questionnaires Forms Completed

Transplant Center	Baseline Forms			6-Month Follow-up Forms			9-Month Follow-up Forms			12-Month Follow-up Forms			15-Month Follow-up Forms		
	Number Exp.	Number Rec.	Percent Rec.	Number Exp.	Number Rec.	Percent Rec.	Number Exp.	Number Rec.	Percent Rec.	Number Exp.	Number Rec.	Percent Rec.	Number Exp.	Number Rec.	Percent Rec.
Univ. of California San Francisco	92	71	77.2	70	61	87.1	47	33	70.2	27	24	88.9	15	14	93.3
Ohio State Univ.	58	48	82.8	49	63	89.6	31	26	83.9	18	12	66.7	11	9	81.8
Univ. of Pittsburgh	84	64	76.2	64	51	79.7	60	44	73.3	40	31	75.5	21	16	76.2
Univ. of Texas Houston	32	25	78.1	25	18	72.0	16	13	81.3	8	7	87.5	4	3	75.0
Univ. of Wisconsin	79	66	83.5	66	58	87.9	48	36	75.0	20	16	80.0	12	10	75.0
Total	345	274	79.4	273	232	85.8	202	152	75.2	113	89	78.8	68	52	82.5

- Follow-up Questionnaires were expected from all patients who had initially agreed to participate in the patient portion of the study unless the patient: (1) failed to return a Baseline Questionnaire, (2) failed to return 2 consecutive Follow-up Questionnaires, or (3) was withdrawn from the study because of death, graft failure, or relocation prior to the end of the particular follow-up period.

A total of 274 completed Baseline Questionnaires were received. The number of patients who completed 6-month, 9-month, 12-month, and 15-month follow-up questionnaires was 232, 152, 89, and 52, respectively.

Data Management and Data Entry

A computerized data management system was used to monitor the various data collection activities. The data management system was developed using the R-Base 5000 software package. Shortly after the patient's transplant surgery, the data collector at the transplant center asked the patient to participate in the study. If the patient agreed, the data collector sent a General Information Form (containing the patient's name, study identification number, mailing address, telephone number, and date of transplant) and the signed consent forms to Battelle. As soon as this information was received, it was entered into the data management file.

The data management file was updated daily during the follow-up data collection period. As Baseline and Follow-up Patient Questionnaires were sent, the date sent was entered into the data management file. As completed Medical Records Information Forms and Patient Questionnaires were received, they were stamped with the date received and this information was entered into the data management file. The file also contained exit information (i.e., date of withdrawal from the study, reason for patient withdrawal).

The data management file served several purposes. The file was used to print mailing labels for sending Baseline and Follow-up Patient Questionnaires. It was also used to generate lists of patients for whom Follow-up Medical Records Information Forms were due to be completed by the data collector at each transplant center. The data management file was used to prepare lists of patients who required follow-up telephone calls (i.e., patients who recently had been sent patient questionnaires, patients who were overdue in returning completed questionnaires). Finally, the file was used to prepare a weekly summary status report listing all forms received for each patient included in the study.

Completed data collection forms were coded and edited manually by a Survey Specialist at Battelle before data entry. Data collection forms were examined for completeness and understanding. Phone calls were made to patients and/or data collectors at the transplant centers to solve the problem of incomplete data. To the extent possible, all data collection forms were designed to consist primarily of closed-ended items that were precoded. However, a few questions (i.e., follow-up physician visits, laboratory and other tests performed, prescription drugs) required manual coding.

After coding, the data were entered with IBM personal computers using a data entry package developed at the Fred Hutchinson Cancer Research Center (Seattle, WA). The program was able to incorporate skip patterns into data entry. It also had the ability to make logical and consistency checks, and to check for out-of-range values. The data entry package required double entry of all data forms, thereby providing 100% verification of all data input. These capabilities resulted in data files that required very little subsequent data cleaning. As necessary, the various computer files for each patient were merged for analysis.

Data Analysis

Analysis of data obtained from the Baseline and Follow-up Medical Records Information Forms and from the Baseline and Follow-up Patient Questionnaires will be largely descriptive in nature. For the purpose of this report, data will be presented for all transplant patients, as well as for patients grouped by primary renal diagnosis (diabetes versus nondiabetes). Patients will also be grouped according to the initial immunosuppressive drug protocol of the center at which their surgery was performed. The two initial immunosuppressive drug protocol groups are: patients receiving cyclosporine and prednisone (CSA + PRED) and patients receiving ayathioprine, prednisone and antilymphocyte globulin (AZA + PRED + ALG). The AZA + PRED + ALG group consists of patients who received transplants at the following three centers: University of California, San Francisco; Ohio State University; and University of Wisconsin. The CSA + PRED group consists of patients who received transplants at the University of Pittsburgh and the University of Texas, Houston.

It is important to recognize that during the period of this study, the University of California, San Francisco, Ohio State University, and the University of Wisconsin used an induction protocol of AZA + PRED + ALG exclusively. Similarly, the University of Pittsburgh and the University of Texas, Houston used an induction protocol of CSA + PRED exclusively. Thus, in grouping transplant centers according to their initial immunosuppressive drug protocols, it is not possible to distinguish the effects of immunosuppressive protocol from other characteristics of the transplant centers that could also influence patient outcomes (what has become known as the "transplant center effect"). To do so would require additional data from larger samples of transplant centers.

CHAPTER 3

CLINICAL IMMUNOSUPPRESSION: A REVIEW

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CHAPTER 3 CLINICAL IMMUNOSUPPRESSION: A REVIEW

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Introduction

Perhaps no area of organ transplantation is as difficult to decipher as immunosuppression (Bach, 1981:89; Brenner and Munro, 1982:268; Benjamin and Leskowitz, 1987; Bach and Sachs, 1987:489; Belzer, 1988:3; Council on Scientific Affairs, 1987:1781; Calne, 1981:44; 1982:91; 1985; Fabre and Ting, 1979:1; Hamburger, 1981:1; Kirkpatrick, 1982:2727; 1987:2993; Nossal, 1987:1320; Obituary, 1987:923; Prowse and Lafferty, 1988:37; Suthanthiran and Garovoy, 1983:315; Stiller and St. C. Sinclair, 1979:251; Stites et al., 1984; Sell, 1987; Toledo-Pereyra, 1988; White, 1983:201). Rejection and infection remain the most significant of both the short- and long-term complications transplant recipients experience. The two are related. If a patient is insufficiently immunosuppressed, the graft will be rejected. If the patient is over-immunosuppressed, they may retain the graft, but become highly susceptible to a variety of infections--viral, bacterial, fungal, protozoan, and nocardial (Rubin et al., 1981:405; Tolkoff-Rubin and Rubin, 1988:445; Rubin, in press). Therefore, while the purpose of immunosuppression is to prevent rejection, its untoward outcome is often infection. Ideally, the goal is to sufficiently immunosuppress the patient, while eliminating, or at least minimizing, the risk of infection. It is generally believed that the more specific the immunosuppressive agent, the greater the likelihood that this therapeutic goal can be achieved. Thus far, the immunosuppressive properties of even the most effective of immunosuppressive agents--cyclosporine--are too general. It is hoped that further syntheses of cyclosporine will produce an analogue that is increasingly specific (see Hoyt et al., 1988:111).

A review of the literature reveals that a wide range of immunosuppressive drugs (e.g., azathioprine, prednisone, cyclosporine) and immunosuppressive techniques (e.g., thoracic duct drainage, blood transfusions, splenectomy, total lymphoid irradiation) have been and continue to be used to induce immunological tolerance (Bell et al., 1983:677; Fish et al., 1983:134; Levin, 1985:1321; Modry, 1983:122; Monaco, 1988:83; Niblack and Richie, 1983:197; Salvatierra, 1988:151; Schulak and Corry, 1988:137; Strober et al., 1979:87; Sutherland et al., 1983:277; 1983:2881; Tilney and Murray, 1967:1204; Tilney and Strom, 1988:118; Waer et al., 1985). The efficacy of some of these agents and techniques has been unequivocally demonstrated, while others are unproven and continue to be the subject of further study. Not surprisingly, the use of these agents and techniques has varied over time and from transplant center to transplant center. For example, initial trials of cyclosporine in Europe often used this agent solely, while in the United States early trials involved cyclosporine in combination with other agents (e.g., prednisone) (Calne et al., 1979:1033; Canadian Multicentre Transplant Study Group, 1983:809; 1986:1219; Carpenter et al., 1981:265; European Multicentre Trial, 1982:57; 1983:986; Keown et al., 1981:686; Rynasiewicz et al., 1981:276; Starzl et al., 1982:819; 1981:486; 1980:17). Further complicating the assessment of effectiveness, is the tendency to administer different agents at different points in time. For example, some drugs and techniques are used preoperatively, others are used operatively, and still others are used perioperatively and postoperatively. Moreover, the quantities of pharmacological agents administered vary considerably over the transplant trajectory. Initially large doses of a variety of agents may be used with tapering according to a maintenance schedule accomplished over time. For example, patients may start with high dose cyclosporine and moderate dose prednisone, with or without other agents, such as antilymphocyte globulin.

All agents may be tapered over time with certain agents eliminated from the maintenance protocol.

What all the foregoing means for transplantation is confusing. Often investigators fail to adequately describe their immunosuppressive protocols when reporting their transplant results. Others may vary their immunosuppressive protocol within a given series of patients. Still others may alter their protocols in the face of intractable rejection and then criticize the protocol applied if positive results are not achieved. Given the central role that immunosuppression plays in the success of transplantation, it is simply unbelievable that standard reporting procedures have not been developed which, at the very least, would facilitate meta-analysis approaches to the examination of data across transplant programs (Bulpitt, 1988:93; Hedges and Olkin, 1985; Light and Pillemer, 1984; Rosenthal, 1984; Sacks et al., 1987:450; 1987:576 Thacker, 1988:1685; Wachter, 1988:1407; Wolf, 1986). Furthermore, it would be highly desirable if the methodology of the clinical trial were uniformly applied to studies that purportedly examine the outcomes of various immunosuppressive protocols. One must entertain the possibility that much greater progress could be achieved in organ transplantation if basic research principles were followed, and the reporting of results was uniform across studies (Bulpitt, 1983; de Saitonge and Vere, 1984; Detsky and Sackett, 1985:709; Feinstein, 1985; Fletcher et al., 1988; Friedman et al., 1981; Kramer and Shapiro, 1984; Meinert, 1986; Pocock, 1984; Pocock et al., 1987:426; Rudicel and Esdaile, 1986:1500; Sackett et al., 1985; Shapiro and Louis, 1983; Weiss, 1986).

Unlike the foregoing suggests, this chapter is not intended to criticize previous studies of immunosuppressive protocols. While this is inevitable in many areas, this chapter is intended to provide a sufficiently wide perspective that the reader can grasp the basic foundation of organ transplantation. Without this foundation, it is impossible to fully appreciate progress in the field, or goals that remain to be achieved.

The remainder of this chapter is divided into several sections. They are: (1) historical developments in immunosuppression, (2) results of cyclosporine (early and late reports), (3) side-effects of agents, (4) the basics of immunosuppressive management, (5) immunosuppressive protocols currently in use, and (6) the role of conversion in cyclosporine protocols.

Historical Developments in Immunosuppression

Historical developments in both experimental and clinical immunosuppression have been reviewed by Bach (1979:89), Calne (1981:44), and more recently by Moore (1988:3), Cerilli (1988:16), Monaco (1988:83), Tilney and Strom (1988:118), and Schulak and Corry (1988:137). These have also been similarly considered by Evans and coworkers in the National Heart Transplantation Study (1984:4-1). Certain aspects of this history are worthy of consideration here since they provide some indication of the magnitude and pace of developments thus far. Although progress has been slow, it has been relatively steady. Cyclosporine, approved by the Food and Drug Administration in November 1983, is clearly the most significant of developments in clinical immunosuppression in the past decade (Macek, 1983:449; Kolata, 1983:40). More recently, however, several additional pharmacological agents have been approved for clinical use or are under testing. These include OKT-3 (Othoclone), a monoclonal antibody, approved by the FDA for the treatment of rejection in June, 1986, and FK506, a macrolide antibiotic obtained from Streptomyces tsukubaensis, strain No. 9993, that was collected from the soil of the Tsukuba area in northern Japan (Goto et al., 1987:4; Ochiai et al., 1988:209; Starzl et al., 1987:1; Tanaka et al., 1988:11; Todo et al., 1988:215; Zeevi et al., 1988:220). In addition, several reports have been published on 15- deoxyspergualin (DSG), a 15- deoxy analogue of the antitumor antibiotic spergualin. DSG has been shown to prolong the graft survival of skin, heart, pancreas islet, kidney, and liver in the rodent (Amemiya et al., 1988:229; Todo et al., 1988:233; Engemann et al., 1988:237; St J. Collier et al., 1988:240). The study reports on OKT-3 have been mixed (Ackermann et al., 1988:242; Burke et al., 1988:252; Delmonico et al., 1988:249; Goldstein, 1988:1; Harford et al., 1988:245; Monaco, 1988:83; Ortho Multicentre Transplant Study Group, 1985:337; Ponticelli et al., 1987:99; Roberts et al., 1987:286; Thistlethwaite et al., 1987:176; Waldman, 1988:154), while FK-506 is showing some promise in experimental studies and initial clinical investigations (see Starzl et al., 1987:1). It is noteworthy that OKT-3 is being used prophylactically by some transplant programs as a replacement for another immunosuppressive agent--antilymphocyte globulin (see Debure et al., 1988:546). This is a relatively new development that was reported upon extensively at the Twelfth International Congress of the Transplantation Society held in Sydney, Australia on August 14-19, 1988. (Much concern was expressed regarding the financial implications of this approach.) At this time, there are no other major developments in the field of clinical immunosuppression, although a further synthesis of cyclosporine--cyclosporine G--is being used experimentally (Hoyt, 1988:111; Wenk et al., 1988:558).

Conventional Approaches to Chemical Immunosuppression

Chemical immunosuppressive agents are synthetic products that have one of two functions--to suppress or depress immune responses. As already noted, their primary function is to minimize or, ideally, eliminate allograft rejection. Surveying the relatively brief history of chemical immunosuppression, one is struck with the significance of research conducted by Schwartz and coworkers (1959:1394) who, in 1958, demonstrated that 6-mercaptopurine (6-MP) could prevent the production of antibodies against bovine serum albumin. Since their early work, other investigators have demonstrated the efficacy of a variety of other agents, but 6-MP (Purinethol) and its imidazole derivative, azathioprine (Imuran), remain among the most frequently used immunosuppressive drugs, even in light of the cyclosporine revolution. Interestingly, because of the nephrotoxicity associated with cyclosporine, multiple immunosuppressive agents are being utilized in increasingly complicated immunosuppressive protocols. Azathioprine remains a stable component of the immunosuppressive armamentarium (Salemans, 1987:217).

Azathioprine was first synthesized in 1961 by Elion and associates (1961:85), 11 years after they had synthesized 6-MP (Elion et al., 1952:411). In vitro, azathioprine inhibits most activities of human lymphocytes. Under certain conditions it also has an anti-inflammatory action (Bach, 1981:89).

There are several major complications associated with the administration of azathioprine (Tilney and Strom, 1988:118). These include: (1) a diverse array of infections and viral disorders, (2) hepatitis, (3) bone marrow aplasia, and (4) malignant diseases. It is well-recognized that azathioprine, as well as some other immunosuppressive agents, may result in the development of malignant tumors. Penn (1979:1047; 1982:71; 1983:2790; 1987:32; 1988:276;

1988:439), who has persisted in following-up the cancer experience of transplant recipients long-term, reports that the incidence of tumors in the transplant recipient population is approximately 100 times greater than that observed in the general population, after controlling for age. The increased potential for malignancy in transplant recipients, particularly the lymphoproliferative disorders, may also relate to drug toxicity. Although cyclophosphamide has been substituted for azathioprine in persons with evidence of hepatocellular damage, it seems clear that those with active hepatitis do not require cytotoxic drug therapy for allograft maintenance; the grafts may continue to function for indefinite periods of time without immunosuppression (Tilney and Strom, 1988:118; Weir et al., 1985:839; Kirkman et al., 1982:347).

Corticosteroids have also played a key role in transplant immunosuppression. In 1950, Germuth and Ottinger (1950:815) first demonstrated that cortisone was a powerful immunosuppressant, and in 1951, Billingham et al. (1951:1157) showed that high doses of cortisone were effective in prolonging skin allograft survival, although the prolongation period was minimal. Similar results were observed with other organ allografts (Zukowski et al., 1963:208). It was soon concluded that corticosteroids were best used in conjunction with other corticosteroids (Bach, 1981:89), in particular the thiopurines (Marchioro et al., 1964:412), nitrogen mustards (Baker et al., 1952:702), and antilymphocyte sera (Hoelm and Simmons, 1967:1409).

There are numerous side-effects associated with the use of steroids (Tilney and Strom, 1988:118). These are basically the same side-effects observed in other situations where steroids are used regularly (Salaman, 1983:118; 1986:304). The seriousness of these complications should not be underestimated. Steroids may, for example, encourage microbial and viral infections. They may also cause gastrointestinal hemorrhage and perforation of gastric ulcers, severe diabetes and bone disorders, especially bilateral asceptic necrosis of the femoral head, which may be crippling (Bach, 1981:89). Serious psychological disorders may develop and persist following withdrawal of therapy. Bach (1981:104) has concluded that "... steroid therapy represents one of the most serious hazards of kidney transplantation." For this and other reasons, transplant teams have experimented with alternate-day steroid therapy. As described by Tilney and Strom (1988:118), because of diurnal variations in the endogenous production of corticosteroids, the time of taking the daily dose may be important. Unfortunately, few data are available on this point, either experimentally or clinically. Several short-term studies have at least suggested that alternate-day steroid therapy may reduce steroid toxicity as well as providing adequate immunosuppression in some transplant recipients (Bell et al., 1972:223; Diethelm et al., 1976:867; Sampson and Albert, 1973:345).

Another immunosuppressive agent, more commonly used in bone marrow transplantation than kidney transplantation, is cyclophosphamide--an alkylating agent. Although a powerful immunosuppressant in mice, it initially met with only a small measure of success in man (Fox, 1964:475). Based on early experience, it was difficult to draw firm conclusions about this agent, primarily because only a relatively small number of cases were available for analysis. As noted by Tilney and Strom (1988:118) there is rather scanty information on the use of cyclophosphamide in clinical transplantation. In 1971, Starzl (1971:70), suggested that the drug might be more effective than azathioprine in renal and liver transplantation, however, follow-up was brief, and no control group was apparent. There have been few other clinical reports, perhaps underscoring the fact that the agent may be exceptionally toxic. Today, the general consensus is that when azathioprine is poorly tolerated, especially because of bone marrow depression, cyclophosphamide may be substituted advantageously.

Antilymphocyte Sera

Metchnikoff (1899:737) made the first antileukocyte serum (ALS) by injecting extracts of rat and rabbit lymph nodes and spleen into guinea pigs. However, it was not until 1955 that the immunodepressive effect of ALS was discovered. Earlier, in 1951, Woodruff and associates (1951:57) had suggested that antilymphocyte sera might be helpful in transplantation. In 1961, Waksman et al. (1961:997) were able to achieve a slight increase in the survival of skin grafts in guinea pigs, but it was not until 1963 that Woodruff and Anderson (1963:702) demonstrated extended survival.

Over the years, a great deal of work has been done on ALS (Barna, 1977; James, 1967:615; Medawar, 1968:501). This work is difficult to review in detail here (see Novick, 1983:253; Monaco, 1988:83). Today, antilymphocyte globulin (ALG) is often used in multiple drug immunosuppressive protocols. The University of Minnesota, for example, continues to administer ALG as part of its standard immunosuppressive protocol, as does Ohio State University. Occasionally, ALG is also administered to reverse a particularly severe rejection episode.

Basically there are two major polyclonal antilymphocyte globulins in use today, only one of which is commercially produced. The first of these, also reported to be the most effective, is Minnesota ALG (MALG). This product was developed at the University of Minnesota and, technically, is not approved for general use by the Food and Drug Administration. Nonetheless, many transplant teams use MALG routinely, and FDA approval is now being sought.

The commercially produced ALG is commonly referred to as ATGAM and is licensed by Upjohn. Although this product is generally believed to be somewhat less effective than MALG, the major problem is actually availability. Supplies are often limited, and transplant teams complain about the uncertainty of being able to obtain adequate quantities of the drug to use it routinely.

There are a variety of other antilymphocyte sera that have been produced and subjected to investigational study. For example, the Stanford University Medical Center has made use of rabbit antithymocyte globulin with a reasonable measure of success (Baumgartner et al., 1979:2; Copeland and Stinson, 1979:4). Other transplant programs have manufactured and used goat and horse antithymocyte globulin. Many of these products have not been as successfully applied as MALG.

More recently, it has been demonstrated that monoclonal antibodies can be used to effectively treat rejection (Kung et al., 1979:347; Ortho Multicentre Transplant Study Group, 1985:337; Monaco, 1988:83). The developments in this area have been exciting, particularly in light of the initial experience of Cosimi and coworkers (1981) with OKT-3, a pan-T antibody recently approved by the Food and Drug Administration for clinical use (Morris, 1983). Initial results indicated that the intravenous administration of OKT-3 eliminated circulating T-lymphocytes within minutes, but often after several days T-lymphocytes expressing the T4 or the T8 determinants, but not T3, reappeared.

Like all immunosuppressive agents, antilymphocyte sera are not without side-effects. First, they are painful and produce an inflammatory reaction at the site of injection (Kashiwagi et al., 1968:275; Traeger et al., 1969:455). Second, in man, some sera provoke thrombocytopenia (Bach, 1981:89) and others produce thrombocytosis, while still others have no appreciable effect on the number and functions of platelets. These findings depend upon both the type and dose of ALS. Third, in man, sensitization to horse protein is common. Bach (1981:89) notes that this may lead to severe complications such as uticaria, malaise with hypotension, sometimes major anaphylactic shock with collapse and respiratory embarrassment and, occasionally, serum sickness. Fourth, ALS may be nephrotoxic, although the evidence remains unclear. Finally, in man, ALS, like azathioprine, may facilitate the development of malignant tumors. Since many transplant recipients receive multiple drugs, however, it is difficult to determine which of the several drugs have a primary role in tumor development.

There are several adverse reactions associated with the administration of Orthoclone OKT-3, as described by Monaco (1988:83). After the first and/or second dose of OKT-3 there are often a number of minor adverse reactions that are both predictable and manageable. The most common early adverse reaction is a self-limited acute febrile syndrome consisting of pyrexia, chills and tremor, occurring in varying degrees in more than 90 percent of the patients. Respiratory systems such as dyspnea, chest pain, and wheezing occur in less than 25 percent of patients, whereas gastrointestinal symptons (e.g., diarrhea, nausea, rarely vomiting) occur in less than one-third of the patients (Monaco, 1988:83).

In addition to the foregoing, some patients may experience insignificant cardiovascular symptoms such as fluid retention, hypotension, hypertension, and/or tachycardia. Fewer than 20 percent of patients show some evidence of transient leukopenia, headache, dizziness, and agitation. Pulmonary edema has been noted in about 5 percent of the patients treated, although modifications in the administration of OKT-3 has virtually eliminated this as an adverse reaction.

OKT-3 administration does not appear to increase the risk of infection over other antirejection protocols. Likewise, there is no evidence that OKT-3 therapy, used as described by Monaco, is associated with an increase in malignant complications posttransplant.

Other Nonspecific Immunosuppressive Techniques

As noted above, a variety of techniques have been used to manipulate the immune system in man (see Schulak and Corry, 1988:137). Some of these have been widely heralded initially, only to be abandoned later. Others seem to come and go, resurrected at times when progress in transplant immuosuppression has been slow. With the use of cyclosporine, an increased interest has arisen as to the possible synergy of the various immunosuppressive techniques when combined with cyclosporine. It is difficult to estimate what role these techniques will play in the immunological future of transplantation. Many of them are not worthy of extended discussion.

Total body irradiation (TBI) is a technique that depresses immune responses. In 1950, Demster et al., first suggested that the technique be applied in transplantation. In fact, in man, TBI was the first method of immunosuppression used in kidney transplantation. It was used at Necker Hospital in 32 patients between 1959 and 1963 (Bach, 1981:89). Unfortunately, Bach reports that a significant number of cases of septicemia developed, forcing TBI to be abandoned in favor of chemical immunosuppression.

Total lymphoid irradiation (TLI) is a technique commonly applied in the treatment of Hodgkins disease and non-Hodgkin's lymphomas (Strober et al., 1979:87; Schulak and Corry, 1988:137). This form of treatment has shown profound immunosuppression that was selective for T-cells (Sutherland et al., 1983:277). TLI appears to be one of the most potent methods of preventing allograft rejection and inducing tolerance to alloantigens in adult animals (Slavin et al., 1978:963; 1979:139; Strober et al., 1979:87; Zan-Bar et al., 1978:1400). This technique has occasionally been applied by the Stanford heart transplant team (Modry et al., 1983:122; Sadeghi et al., 1983:209). In addition, the University of Minnesota transplant team has also used it in conjunction with cyclosporine (Sutherland et al., 1983:460).

While there is growing experience with experimental TLI, the largest series has been reported by Najarian and colleagues (1982:442). In this series, TLI was reserved for retransplantation patients who suffered early immunologic loss of their previous renal allograft (Schulak and Corry, 1988:137). TLI was complicated by leukopenia, nausea, vomiting and infection. Transplantation followed as soon as possible, depending upon organ availability, in most cases this was accomplished in less than 40 days. Others who have successfully used TLI include Cortesini and associates (1985:1291), Vanrenterghem and colleagues (1984:636), and Sampson and coworkers (1985:1299).

In summary, both laboratory and clinical evidence demonstrate that TLI is a potent method of immune manipulation (Schulack and Corry, 1988:137). With TLI, concomitant pharmacologic immunosuppression may be either reduced or curtailed, even in what are generally assumed to be high-risk patients. A significant disadvantage associated with TLI, however, is the necessity of acquiring a crossmatch negative organ within a relatively short period of time following completion of radiotherapy. For this reason TLI may be better suited to living-related donors rather than cadaveric kidney transplantation. Nonetheless, Schulak and Corry (1988:137) suggest that additional clinical studies are necessary in order to better define both the optimal radiation-immunosuppression regimen and the long-term morbidity before TLI can be endorsed for widespread use.

Thoracic duct drainage (TDD) is yet another technique that has attracted considerable attention over the years. Tilney and Murray (1967:1204) initially advocated the use of this technique. In France, Revillard (1970:703) exhibited similar enthusiasm. Periodically there has been renewed interest in the merits of thoracic duct drainage, although the technique is, for the most part, rarely used (Bell et al., 1983:677; Niblack and Richie, 1983:197). Bach (1981:89) has concluded that "... it is difficult to judge the effect of this procedure on allograft tolerance. At best, it can only be one auxiliary method."

Based on their review of TDD, Schulak and Corry (1988:137) conclude that it is an effective method for achieving at least short-term manipulation of the immune response by significantly depleting the host of circulating T-lymphocytes and by decreasing immunoglobulin levels, albeit if only through dilution. Consequently, early renal allograft survival has been improved in most clinical trials of TDD. It is not yet clear whether TDD has a long-term effect on graft survival. On the negative side, TDD is relatively difficult to perform, is cumbersome to both the patient and nursing staff, and greatly prolongs hospitalization if used prior to transplantation. Not surprisingly, therefore, TDD is not being endorsed or used widely at this time.

There has been some interest in the immunological properties of splenectomy (Krohn, 1953:21). Ungar indicated that by reducing the mass of lymphoid tissue, grafts may be tolerated better with a reduced possibility of rejection (Krohn, 1953:21; Kountz and Cohn, 1962:59). Bach (1981:89) has concluded that there is little evidence that routine splenectomies improve graft survival by making immunosuppressive drugs more effective. Nonetheless, at least one major transplant program in the United States--the University of Minnesota--periodically splenectomizes patients as part of their standard immunosuppressive protocol (Najarian et al ., 1983:2463).

The major drawback to the use of splenectomy is sepsis. Typically patients have a fulminant course with systemic toxicity, fever, chills, vascular collapse, and a rapid demise (Schulak and Corry, 1988:137). Many of these complications occur in the long-term. Studies with short-term followup have failed to show these. The increased risks long-term are apparent for both children and adults. Also noteworthy is the fact that patient survival after two years is apparently jeopardized by splenectomy (Alexander et al., 1984:467).

Schulak and Corry (1988:137) conclude that "... splenectomy cannot be generally advised as a method for manipulating the immune response in transplant patients." Nevertheless, they indicate that the use of splenectomy may be prudent in patients with hypersplenism and persistent azathioprine-associated leukopenia and in candidates for transplantation when use of cyclosporine and/or ALG is precluded.

Blood transfusions prior to transplantation have also been demonstrated to prolong graft survival (Berg *et al*., 1982:344; Cecka, 1987:287; Editorial, 1984:830, Ettenger *et al*., 1983:943; Feduska *et al*., 1984:704; Glass *et al*., 1985:615; Kerman *et al*., 1983:50; Light, 1984:917; Lundgren *et al*., 1986:66; Mendez *et al*., 1984:946; Morris, 1984:98; Opelz *et al*., 1987:239; Persijn, 1985; Persijn *et al*., 1984:1043; Salvatierra, 1988:151; Salvatierra *et al*., 1985:654; 1983:243; 1983:181; 1983:924; Sollinger *et al*., 1984:612; Terasaki *et al*., 1983:1065; Tokunaga and Terasaki, 1986:634; van Rood, 1983:915; Yamauchi *et al*., 1983:932). Dialysis patients who have received blood transfusions and later were transplanted have been found to have better graft survival rates than patients not given transfusions (Morris, 1983:273). In fact, Terasaki and coworkers (1983:1065), who were first to report on the beneficial effects of blood transfusions, have recently reconsidered the impact of pretransplant blood transfusions on graft survival rates. They note that graft survival rates showed a steady decline from 1968 to 1975 but subsequently improved at a rate of 2.4 percent per year for parent donor transplants and 2.7 percent per year for cadaver donor transplant. During this period of improving survival rates, the pretransplant transfusion exposure rate increased from 52.0 percent in 1977 to 91.0 percent by 1981. This led Terasaki and coworkers (1983:1065) to conclude that "... transplantation has now reached a new level of acceptability as a clinical treatment modality and that blood transfusion has produced its effect on graft survival when results are disseminated over a large number of transplant centers."

Blood transfusions have been both donor and nondonor specific. The results reviewed above are largely characteristic of nondonor specific transfusions. The results of donor-specific transfusions are actually more remarkable, and are also worthy of consideration (Mendez et al., 1984:946).

In 1978, Salvatierra and coworkers first introduced pretransplant donor-specific blood transfusions (DST) in "... an attempt to select potentially successful transplants from among immunologically disparate related donor-recipient pairs" (Salvatierra et al., 1983:243; 1983:181). Early results were very positive and subsequent results from a larger experience with DST has demonstrated the efficacy of this procedure at the University of California--San Francisco, as well as other centers that have adopted this protocol (Yamauchi et al., 1983:932; Sollinger et al., 1984:612; Ettenger et al., 1983:943). The only truly significant problem associated with DST has been an "... unfavorable degree of sensitization," currently estimated to be about 30.0 percent. Light and coworkers (1984:917) have reported on one approach to eliminate the risk of sensitization--drawing one donor unit, dividing it into three aliquots, and administering transfusions as 1/3 unit at 1, 3, and 5 weeks following blood donation.

Recently, the use of cyclosporine has called into question the efficacy of blood transfusions (Niessen et al., 1984:339), despite the fact that the European Multicentre Trial Group's (1983:986) comparison of cyclosporine with azathioprine and prednisolone found that nontransfused patients had a better graft survival than did multiply transfused patients in the cyclosporine group. In the dog model, Niessen and coworkers (1984:339) concluded that: "During the cyclosporine period no difference in graft survival was observed between transfused and nontransfused littermates." Yet, in concluding their analysis, Niessen et al. (1984:339) recommended that: "It might be rewarding to transfuse patients just in case conversion, temporary or otherwise, from cyclosporine to conventional immunosuppression proves necessary..."

Most recently, an editorial appeared in The Lancet regarding the value of pretransplant blood transfusions (Editorial, 1988:567). The editorial pointed out that in a 1986 literature survey conducted by Opelz, nearly 400 publications on the transfusion effect in both clinical and experimental organ transplantation could be identified (Opelz, 1987:3557). It also noted that data from the Collaborative Transplant Study (CTS) showed that actuarial survival rates of first cadaver grafts in patients who had received a transplant in 1982 and 1983 and who had been treated with azathioprine and steroids improved from 50 percent in nontransfused to 65 percent in transfused patients (Opelz, 1985:1015; 1987:3557). The editorial concluded that the mechanism of this nonspecific graft tolerance was unknown at the time and remains unknown at this time, although several hypotheses were suggested: induction of suppression cell response, clonal deletion at time of grafting, and active immunological responsiveness induced by anti-idiotypic antibodies (Burlingham et al., 1987:41). A detailed analysis of the blood transfusion effect proved interesting. Basically, the more transfusions given, the greater the benefit, however, the difference between one and none was most striking, with subsequent transfusions having only a weak additional benefit (Opelz, 1987:3557; Melzer et al., 1987:61).

The editorial goes on to point out that the presence of a transfusion effect remains highly controversial. Some studies still show a beneficial effect (Opelz, 1987:3557; Melzer et al., 1987:61), while other studies indicate excellent results in the absence of transfusion (Perloff, 1986:29; Groth, 1987:153). However, in 1986 at the XIth International Congress of the Transplantation Society, Opelz, reporting the CTS results, announced that the blood transfusion effect with cyclosporine seemed to have disappeared. Since 1982, there had been a steady improvement in one-year graft survival from 60 percent to 80 percent in untransfused patients receiving cyclosporine, so that by 1985 there was no significant difference between transfused and nontransfused recipients. The Lancet editorial points out that "... while this result could be understood, it came as something of a surprise to hear that the beneficial effect in recipients treated with azathioprine also seemed to have disappeared. In the same period, the numbers of patients who were receiving azathioprine but not blood transfusions were small, but the first cadaver graft survival times had steadily improved from 50 percent to 70 percent at one year."

With respect to donor-specific transfusions (DST), the editorial also raised some interesting questions. DST was originally devised to achieve a better outcome from one-haplotype, mixed lymphocyte culture-reactive donors. Because the initial results were excellent, DST was also offered to zero-haplotype transplant recipients. Graft survival in over 200 zero and one-haplotype related grafts, excluding nondiabetics, was 97 percent at one-year. The majority of these recipients had received azathioprine and prednisone (Salvatierra et al., 1987:160). Unfortunately, after DST, some recipients became sensitized, even when concomitant azathioprine was given (Anderson et al., 1984:664). According to the editorial, the question now is whether cyclosporine-treated one-haplotype transplant recipients will do as well as those receiving DST. Data from the CTS for one-haplotype transplants, for example, showed no difference when third party transfusions were compared with DST. Both groups achieved 90 percent one-year graft survival. The conclusion, therefore, arrived at by the author is that "Preoperative transfusions do not confer any benefit on first grafts, but may have a small beneficial effect on regrafts treated with cyclosporine."

The editorial concludes with an expression of uncertainty as to the value of pretransplant blood transfusions (also see Lundgren et al., 1986:1248; Halasz et al., 1987:1001). Concern is expressed over the risks of blood transfusions given the fact that graft survival rates are now within the 80-85 percent range without transfusions.

Salvatierra (1988:151) remains optimistic as to a beneficial effect associated with transfusions He notes that pretransplant blood transfusions appear to have a definite role in improving the graft survival of both cadaver and living-related organs in kidney transplantation. He concludes that even in the cyclosporine era there appears to be evidence of a saluatory effect of transfusions in cadaver transplantation. Salvatierra also observes that the DST protocol has allowed the use of living donors with excellent results--results similar to those achieved with HLA-identical sibling transplantation.

The foregoing is but a brief summary of the development and use of selected immunosuppressive drugs and techniques. Because cyclosporine represents, perhaps, the single most important advance in transplant immunosuppression, it is more carefully evaluated below. We begin with a discussion of the discovery of cyclosporine and then proceed with a discussion of both early and late results based on several major clinical trials conducted in the United States and abroad.

Cyclosporine

The immunosuppressive properties of cyclosporine were first described by Borel in 1976, although the drug itself was discovered in 1972 (Borel, 1976:468; 1982:5; Borel et al., 1983:1881; Morris, 1981:349; White, 1982; Flechner, 1983:263; Moore, 1988:3). Cyclosporine-A, as the drug was then referred to, is a cyclic peptide (11 amino acids) which was initially used as an antifungal agent. Borel and Schwartz (1964) via routine screening, noticed that cyclosporine-A exerted a variety of immunosuppressive responses in rodents and guinea pigs. Gradually, studies in animals and man confirmed the immunosuppressive properties of cyclosporine. A review of the history of cyclosporine, adapted from Borel (1983:2219) is provided in Table 3-1.

The first clinical trials of cyclosporine began in 1978. These trials involved the use of cyclosporine in bone marrow transplantation (for the treatment of graft-versus-host disease) and also in renal transplantation (Beveridge, 1983:433). These initial experiences have been described by Calne and coworkers (1982:347) and Powles et al. (1982:485) in a book edited by White (1982) summarizing the "proceedings of an international conference on Cyclosporine A" held in Cambridge in September, 1981.

Calne's initial trial with cyclosporine took place between June, 1978 and May, 1979 and included 16 cadaveric kidney transplants. It was during this trial that Calne and his coworkers began to suspect that cyclosporine was nephrotoxic in man, although animal studies had shown no evidence of nephrotoxicity. The starting dose, as described by Calne, was 25 mg/kg for the first seven patients. In this group, only one patient had primary and continuing renal allograft function, the remainder had early posttransplant anuric and oliguric episodes. At this time it was thought that, despite the

Table 3-1
Review of the History of Cyclosporine

Date	Key Person(s)	Event
1970	B. Thiele	Isolation of new strains of fungi impeficti producing antifungal metabolities.
1970	Z.L. Kis *et al*.	Isolation of a metabolite mixture and characterization as novel neutral polypeptides.
1971	Haerri/Ruegger	Isolation of the partially purified two component metabolite mixture (24-556) on a preparative scale for initial biologic screening.
1972	Borel	Discovery of immunosuppressive properties of metabolite 24-556 in rodents.
1973	Ruegger	Purification of CSA (27-400).
1973	Dreyfuss *et al*.	Culture and production of CSA.
1974	Borel *et al*.	Animal studies of the immunosuppressive activity of CSA, in vivo and in vitro.
1975	Petcher *et al*. Ruegger *et al*.	Elucidation of the structure of CSA (X-ray studies and chemical degradation).
1976	--	Toxicity studies (rats, monkeys) demonstrate selectivity of CSA for lymphocytes and lack of effect of hemopoiesis.
1976	--	Worldwide confirmation of specific immunosuppressive effect of CSA in experimental transplantations and other models.
1978	Calne *et al*. Powles *et al*.	First clinical trials (kidney transplantation, graft versus host disease).
1980	Wenger	Total synthesis of CSA (Ruzicka Award presented in 1982).

Table 3-1 (Continued)
Review of the History of Cyclosporine

Date	Key Person(s)	Event
1981	Bueding *et al.* Thommen	Publication of antischistosomal and antimalarial activity of CSA. CSA symposium at Trinity Hall, Cambridge
1983	--	Sandimmune first registered in Switzerland.
1983	--	First International Congress on Cyclosporine, Houston, Texas.
1983	--	Approval of cyclosporine by the U.S. Food and Drug Administration.
1987	--	Second International Congress on Cyclosporine, Washington, D.C.

Adapted from Borel, 1983:2222.

lack of biopsy evidence, the poor renal function had an immunological etiology. Therefore, either Cytimun (a cyclophosphamide analogue), steroids, or both were added to the immunosuppressive protocol. After several months, convinced that cyclosporine was nephrotoxic, and in an attempt to avoid this, Calne reduced the starting dose to 10 mg/kg in the next five patients, three of whom still had primary anuric phases and four required the additional steroid therapy for (histologically proven) severe rejection of the graft. Calne then adopted a protocol using a starting dose of 17.5 mg/kg of cyclosporine. Even at this dose, Calne and his coworkers found that both rejection episodes and nephrotoxicity could still occur. The patients who had performed best were the ones in which posttransplant anuria had not occurred.

Based on this early experience, Calne et al. went on to further modify their immunosuppressive protocol, intent upon avoiding excessive immunosuppression and reducing the incidence of postoperative anuria. In their subsequent experience Calne et al. found it necessary to occasionally "switch" patients from cyclosporine to conventional immunosuppressive therapy.

Shortly after Calne's early experience, numerous clinical trials involving cyclosporine began. In 1983 Beveridge estimated that cyclosporine was being clinically tested in more than 100 centers in 19 countries. Over 1,600 patients were reported to have received the drug. Two major multicenter trials were underway--the European Multicentre Trial (1982:57; 1983:986; Johnson, 1986:1229) and the Canadian Multicentre Study Group Trial (1983:809; Stiller et al., 1983:1886). In addition, the University of Minnesota (Najarian et al., 1983:438) and the University of Pittsburgh (Starzl et al., 1982:365) had embarked upon major trials as well, as had the Australians (Sheil et al., 1982:387; 1983:2485; Australian Multicentre Trials Group, 1986:1236). These were, of course, in addition to the trial underway at the University of Cambridge (Morris et al., 1982:355).

A review of the results of these early trials is of some value. In 1984, upon evaluating the early trials, Evans (1984:127) concluded that the results of the various trials were very inconsistent. There was not, as it were, a common story line. In examining the results of the trials, Evans cautioned that few of the published studies on cyclosporine were truly controlled clinical trials, instead they were uncontrolled trials with historical controls. This means that the comparisons between immunosuppressive drug regimens in these early trials were not as precise as one would have hoped. For example, both the Canadian Trial and the European Trial permitted each participating center to use the "best available local therapy" as the conventional therapy. Thus, conventional therapy consisted of more than just azathioprine and prednisone in many instances. Also, some studies, such as those at the University of Minnesota and the University of Pittsburgh, as well as the Canadian Trial, supplemented cyclosporine with prednisone. Only the European Trial used cyclosporine as the sole immunosuppressive agent.

Many of the early trials were further complicated by drug switching. Patients who did not fare well on cyclosporine initially, were permitted to switch to conventional therapy. In the Canadian Trial, for example, 12 cyclosporine-treated patients were switched to standard therapy between two days and fifteen months after transplantation. In the European Trial, 24 of 84 patients in the cyclosporine group with functioning grafts at one year were switched to conventional therapy. In the Cambridge study, of the 79 patients initially given cyclosporine, 12 (15.2 percent) were switched to conventional therapy from 4 days to 34 months after transplantation (Merion et al., 1984:148). In only one of the early trials were patients permitted to go from conventional therapy to cyclosporine, due to the numerous side-effects associated with the long-term use of steroids, particularly osteoporosis. In the Cambridge study, three (10.3 %) of the 29 patients initially treated with azathioprine and steroids were switched to cyclosporine three to eight weeks after engraftment (Merion et al., 1984:148).

Given the foregoing variances in the initial cyclosporine trials, Table 3-2 summarizes the results of these trials with respect to four outcomes--patient survival, graft survival, infections, and rejection episodes. As shown, only with respect to patient survival were the initial trials consistent. Cyclosporine did not improve the survival of transplant recipients. Three out of the five trials found improved graft survival for patients receiving cyclosporine. Finally, although not reported upon by all investigators, infection and rejection episodes varied across trials.

Despite what appears to be inconclusive evidence that cyclosporine had immunosuppressive properties superior to those of conventional immunosuppressive therapy, the Food and Drug Administration in November, 1983 granted approval for the clinical use of cyclosporine. In some respects, this decision might have been considered premature. However, the results of later studies began to converge, indicating that cyclosporine was, indeed, a superior immunosuppressive agent, particularly when used in combination with other immunosuppressive agents.

Just how far kidney transplantation has progressed can only be appreciated by looking at current results in comparison with past results.

Table 3-2
Summary of Findings of Five Early Clinical Trials Comparing Cyclosporine With Conventional Immunosuppressive Therapy

	Drug Protocol		Patient Survival	Graft Survival	Infections	Rejections
Reference to Clinical Trial	Conventional Therapy	Cyclosporine	Higher on Cyclosporine?	Higher on Cyclosporine?	Lower on Cyclosporine?	Lower on Cyclosporine?
University of[1] Cambridge	Azathioprine Prednisone	Cyclosporine Only	No	No	No**	No
Canadian Trial[2]	"Best Available Local Therapy"	Cyclosporine Only	No	Yes*	No	No
European Trial[3]	"Own Best Conventional Protocol"	Cyclosporine Only	No	Yes	No	NR
University of[4] Minnesota	Antilymphocyte globulin (ALG) Azathioprine Prednisone	Cyclosporine and Prednisone	No	No	Yes	Yes
University of[5] Pittsburgh	Azathioprine Prednisone	Cyclosporine and Prednisone	No	Yes	Yes	NR

*YES = Difference is statistically significant.

**NR = Not Reported in literature cited in the text.

[1] Merion et al., 1984:148

[2] Canadian Multicentre Transplant Study Group, 1983:809

[3] European Multicentre Trial Group, 1983:986

[4] Najarian et al., 1983:438

[5] Hakala et al., 1983:465

Most frequently the results of primary interest are graft and patient survival. Since cyclosporine has had a negligible impact upon patient survival, the focus here will primarily be on graft survival.

Table 3-3, as reported by Lowrie and coworkers (1973:863), indicates cadaveric kidney transplant graft and patient survival rates during the period 1966 through 1971. As shown, between 1966 and 1971 there was a 10 percent improvement in graft survival and a 4 percent improvement in patient survival. Interestingly, however, during this time period a decline was experienced in both graft and patient survival for certain years. For example, graft survival rates declined from 40 to 38 percent between 1966 and 1968, while patient survival declined from 76 to 62 percent during the same time period. Clearly, the decline was more profound for patient survival than graft survival.

A later report on survival, based on data for 1977 and 1978 obtained by the Standards Committee of the American Society of Transplant Surgeons (1981:1330), reveals that between 1971 and 1978 there was an overall improvement of about five percent in cadaveric graft survival and a nine percent improvement in patient survival. These results, along with those for various other patient groups, are summarized in Tables 3-4 and 3-5.

Now recall that the early clinical trials with cyclosporine began in 1978. Calne's initial experience at Cambridge demonstrated a marked improvement in graft survival based on 34 patients (Calne et al., 1979:1033). Survival probability at one year improved from a previous 50-55 percent with conventional therapy to 86 percent (including 5 patients out of 34 with functioning grafts who were converted to azathioprine and steroids).

Table 3-3

Cadaveric Kidney Transplant Graft and Patient Survival Rates: 1966-1971

	One Year Survival	
Year	Graft	Patient
1966	40%	76%
1967	41%	60%
1968	38%	62%
1969	54%	70%
1970	52%	71%
1971	50%	80%

SOURCE: Lowrie *et al*., 1973:866.

Table 3-4
Cadaveric Kidney Transplant Graft Survival Rates, 1978

Patient Group	Total Number of Cases	Mean Number of Cases Per Center	Mean Center Survival Rates: 1 Month, Percent	Mean Center Survival Rates: 1 Year, Percent
Living Related	305	43.6	92.2±7.6	78.6±8.5
Nondiabetic Aged ≤50 yr.	253	36.1	93.3±6.5	80.0±8.1
Aged >50 yr.	15	2.1	77.2±43.6*	67.6±40.9*
Diabetic	37	5.3	92.3±10.7	68.7±34.3
Cadaver	576	82.3	83.0±11.8	55.0±5.7
Nondiabetic Aged ≤50 yr.	407	58.1	83.4±9.0	56.3±6.5
Aged >50 yr.	89	12.7	80.9±19.4	49.4±22.7
Diabetic	80	11.4	90.1±19.6**	58.0±35.7**

*Only five centers performed living related transplants in patients older than 50 years.

**Three centers performed only two cadaver transplants each. Actual one-month and one-year graft survival for the 80 transplants performed was 78% and 49%, which primarily reflects results in larger centers.

SOURCE: American Society of Transplant Surgeons, 1981:1331.

Table 3-5
Cadaveric Kidney Transplant Patient Survival Rates, 1978

Patient Group	Total Number of Cases	Mean Number of Cases Per Center	Mean Center Survival Rates 1 Month, Percent	Mean Center Survival Rates 1 Year, Percent
Living Related	305	43.6	98.1±3.8	95.1±3.7
Nondiabetic Aged ≤50 yr.	253	36.1	98.9±1.9	95.9±3.9
Aged >50 yr.	15	2.1	80.0±44.7*	77.2±43.6*
Diabetic	37	5.3	100.0±0.0	89.0±18.5
Cadaver	574	82.0	97.6±1.7	88.6±7.7
Nondiabetic Aged ≤50 yr.	405	57.9	98.2±1.5	90.6±8.0
Aged >50 yr.	89	12.7	97.0±4.3	81.9±11.9
Diabetic	80	11.4	95.1±6.1**	92.5±10.2**

*Only five centers performed living related transplants in patients older than 50 years.

**Three centers performed only two cadaver transplants each. Actual one-month and one-year patient survival for the 80 transplants performed was 90% and 85%, respectively, which primarily reflects results in larger centers.

SOURCE: American Society of Transplant Surgeons, 1981:1331.

In Calne's experience, 32 percent of the patients never required adjuvant steroid therapy (Calne et al., 1981:934).

At Pittsburgh, the early experience of Starzl was similar (Starzl et al., 1981:486), although, as noted previously, Starzl combined steroids with cyclosporine. In his study, Starzl achieved a graft survival rate of nearly 80 percent in a series of 66 consecutive patients followed up for 9-18 months. In the European Multicentre Trial there was also a remarkable improvement in survival when patients receiving cyclosporine alone were compared with those on azathioprine and prednisone. After a followup period of up to 11 months, graft survival estimates were 73 percent in the cyclosporine group and 53 percent in the azathioprine group. As noted above, however, 17 percent of the cyclosporine group with functioning grafts had been switched to conventional therapy, but 27 percent had never received steroids (European Multicentre Trial, 1982:57).

More recently, the results of the one-year followup for the European Multicentre Trial Group (1983:986) have been reported. At the time of this report, 232 recipients of renal transplants at eight European centers were available for analysis. One hundred seventeen (117) patients received cyclosporine as the sole immunosuppressive agent with short courses of intravenous methylprednisolone for the treatment of rejection episodes. One hundred fifteen (115) patients received azathioprine and prednisone for immunosuppression. Graft survival at one-year in the cyclosporine group was 72 percent and 52 percent in the conventional group. One year patient survival in the cyclosporine group was 94 percent and 92 percent in the conventional group.

The Canadian Multicentre Study corroborates the results of previous studies. In their first major report, the Canadian Multicentre Transplant Study Group (1983:809) reported that both patient and graft survival rates differed in the 209 patients available for study. Only graft survival, however, was significantly different. Predicted graft survival at one year was 80.4 percent in patients receiving cyclosporine and 64.0 percent in those receiving conventional therapy (p = .003). Predicted patient survival at one-year was 96.6 percent in patients receiving cyclosporine and 86.4 percent in those given conventional therapy. In addition, the authors of this report indicated that among cyclosporine patients, graft survival was affected detrimentally if the kidney was perfused by machine for longer than 24 hours or if the surgical anastomosis took longer than 45 minutes. The conventional group positively benefitted from five or more blood transfusions.

In a subsequent report, the Canadian Multicentre Transplant Study Group (1986:1219) indicates that at three-years graft survival was 69 percent in the cyclosporine-treated patients and 58 percent in the controls (azathioprine, prednisone, with or without ALG) (p = .05). Patient survival after three years was 90 percent in the cyclosporine group and 82 percent in the control group (p = 0.04).

The Cambridge group (Merion et al., 1984:148) in its major report concluded that although patient survival was better with cyclosporine than conventional therapy, the difference was not significant. They report that at one-year actuarial patient survival in the cyclosporine group was 88 percent, as compared with 76 percent in the group receiving conventional therapy. At three-years, patient survival was 86 and 76 percent, respectively.

With regards to graft survival, at one year, the Cambridge group reported 77 percent for the cyclosporine group and 62 percent in the group receiving conventional therapy. At three-years, graft survival was still 62 percent in the group treated with conventional therapy, whereas it was 70 percent in the cyclosporine group. However, the investigators note that these differences were not statistically significant.

In addition to the foregoing multicenter controlled studies, there have been some rather large single center controlled studies conducted as well. For example, Hakala et al. (1983:465) at the University of Pittsburgh provided an early report of a randomized study of 41 "high-risk" patients, 21, of whom were randomized to cyclosporine and prednisone and 20 to azathioprine and prednisone. All patients had received at least three units of type-specific whole blood prior to transplant. One-year graft survival for the cyclosporine group was 91 percent, and for the azathioprine group, 56 percent.

Najarian and coworkers at the University of Minnesota reported the results of their early prospective randomized trial of 137 patients comparing cyclosporine and prednisone with conventional therapy in 1982 in Brighton, England (see Najarian, 1983:438). Based on their analysis, they concluded that there were "... no significant differences in patient or graft survival when the two groups were compared, no matter what the donor source or the presence or absence of diabetes." Overall graft survival at 22 months was 83.5 percent with cyclosporine therapy and 82.3 percent with conventional therapy. Cadaveric donor organs had 84 percent survival for cyclosporine, and 80 percent graft survival for conventional therapy.

Table 3-6 summarizes the graft survival rates reported in each of the foregoing trials. As shown, there is considerable variation among the trials,

Table 3-6
Summary of Cadaveric Kidney Transplant Graft Survival Rates as Reported in Initial Cyclosporine Clinical Trials

Author	Location	Study Design	Immunosuppressive Protocols	Overall 1 Year Graft Survival
Calne, et *al*., 1979:1033	Cambridge, England	OBS	CSA	85%
			AZA+PRED	58%
Starzl *et* *al*., 1981:486	Denver, CO Pittsburgh, PA	OBS	CSA+PRED	80%
			AZA+PRED+TDD	75%
			AZA+PRED	43%
Canadian Multi-centre Group, 1983:809	Canada	RCT	AZA+PRED+?	64.0%
			CSA+PRED	80.4%
Hakala *et* *al*., 1983:465	Pittsburgh, PA	RCT	AZA+PRED	56%
			CSA+PRED	91%
European Multi-centre Group, 1983:986	Europe	RCT	AZA+PRED	52%
			CSA	72%
Najarian, *et* *al*., 1983:438	Minneapolis, MN	RCT	AZA+PRED+ALG	80%
			CSA+PRED	84%
Merion *et* *al*., 1984:148	Cambridge, England	RCT	AZA+PRED	62%
			CSA	77%

OBS = observational study (not randomized).
RCT = randomized controlled trial.
TDD = thoracic duct drainage

however, a graft survival rate of approximately 80 percent appears to be an attainable goal. With the exception of the University of Minnesota, one-year graft survival rates for patients receiving conventional therapy are in the 50 to 60 percent range.

At the First International Congress on Cyclosporine, Borel (1983:2219) summarized the full range of results from ongoing clinical trials of cyclosporine in Europe, Australia, and North America. The data presented by Borel are reproduced here as Table 3-7. Based on these studies, Borel offered the following observations: "A common feature of these studies was the decrease in the number of rejection episodes seen in cyclosporine-treated patients. When rejection episodes did occur, they were readily resolved with rejection therapy."

Now we ask, how have things changed since these initial trials? First, as noted, in 1983, the First International Congress on Cyclosporine was convened in Houston, Texas on May 16-19. Second, every two years a landmark event is held in transplantation--the meeting of The Transplantation Society. To evaluate possible changes in graft survival rates according to various immunosuppressive protocols, we have reviewed the issue of Transplantation Proceedings that contains the papers and abstracts presented at the First International Congress on Cyclosporine, as well as the Proceedings of three separate International Congresses of the Transplantation Society. We have done this for the Brighton (1982) conference, the Minneapolis (1984) conference, and the Helsinki (1986) conference. For an interim perspective leading up to the Sydney (1988) conference, we have reviewed two additional issues of Transplantation Proceedings. The first contains papers presented at the International Organ Transplant Forum held

Table 3-7

Results of Initial Multicenter Cyclosporine Clinical Trials

	Cyclosporine Group		Control Group	
Group of Studies in	Number of Patients	One Year Graft Survival	Number of Patients	One Year Graft Survival
Europe and Australia	278	55-78%	279	49-73%
North America	251	71-90%	266	53-82%
Europe Multicentre	114	73%	114	53%
Canadian Multicentre	103	80%	106	64%

SOURCE: Borel, 1983:2224.

September 8-11, 1987 in Pittsburgh, Pennsylvania, honoring Dr. Thomas E. Starzl. The second contains papers presented at the Second International Congress on Cyclosporine held in Washington, D.C. on November 4-7, 1987.

Numerous papers were presented at the First International Congress on Cyclosporine reporting on the results of a wide variety of clinical trials. Many of these trials compared cyclosporine protocols with conventional immunosuppressive protocols. These trials include both randomized prospective studies, as well as observational investigations. The studies often were reasonable, but many were methodologically flawed. In general, the studies showed improvement in one-year graft survival rates, although the findings, as discussed previously, were by no means consistent. In some trials, conventional therapy actually had an advantage over cyclosporine (Table 3-8).

At the Brighton meeting, as shown in Table 3-9, only two papers were presented that explicitly addressed differences in patient outcomes according to immunosuppressive protocols. Although other papers were presented addressing a variety of issues related to immunosuppression, only the papers by Najarian and Hakala contained information on graft survival rates by immunosuppressive protocols for a reasonably large number of patients. This undoubtedly reflects the fact that many transplant programs throughout the world did not initiate clinical trials until 1980 or later. Because of this, many centers that were using cyclosporine probably had incomplete data or relatively small numbers of patients that were not worthy of presentation.

The Minneapolis conference in 1984 produced a wider range of papers covering many different immunosuppressive protocols. In fact, a review of these papers often produces confusion and a general sense that many of the studies were poorly designed without suitable controls.

Table 3-8
Summary of Graft Survival Rates for Renal Transplant Recipients as Presented at the First International Congress on Cyclosporine, May, 1983

Author	Location	Study Design	Immunosuppressive Protocols	Overall 1 Year Graft Survival
Starzl et al., 1983:2459	Denver, CO Pittsburgh, PA	OBS	CSA+PRED (CO) CSA+PRED (PA) AZA+PRED (PA)	79% 89.5% 50%
Najarian et al., 1983:2463	Minneapolis, MN	RCT	AZA+PRED+ALG CSA+PRED	80% 87%
Kahan et al., 1983:2469	Houston, TX	OBS	AZA+PRED CSA+PRED	51% 81%
Stiller et al., 1983:2479	Canada	RCT	AZA+PRED+? CSA+PRED	67.0% 83.5%
Sheil et al., 1983:2485	Australia	RCT	AZA+PRED CSA	70% 70%
Halloran et al., 1983:2513	Canada	RCT	AZA+PRED+ALG CSA+PRED	92% 74%
Land et al., 1983:2517	Munich	OBS	CSA+METHYLPREDNISOLONE AZA+PRED	70% 50%
McMaster et al., 1983:2523	Birmingham, England	RCT	CSA+PRED AZA+PRED	77.2%* 85%
Buzendahl et al., 1983:2531	Hannover, West Germany	OBS	CSA+PRED	73%

*Followup is less than one-year.

Table 3-9
Summary of Kidney Transplant Graft Survival Rates as Presented at the Ninth International Congress of the Transplantation Society, Brighton, England 1982

Author	Location	Study Design	Immunosuppressive Protocols	Overall 1 Year Graft Survival
Najarian *et al.*, 1983:438	Minneapolis, MN	RCT	AZA+PRED+ALG CSA+PRED	80% 84%
Hakala *et al.*, 1983:465	Pittsburgh, PA	OBS	AZA+PRED CSA+PRED	56% 91%

RCT = randomized controlled trial.
OBS = observational study

As shown in Table 3-10, multiple drug immunosuppressive protocols were a major focus of study. Some centers in Europe continued to administer cyclosporine as the sole immunosuppressive agent, something that never really caught on in the United States. As indicated, for the most part, cyclosporine protocols produced graft survival rates of 80 percent or better, while conventional protocols were in the 50 to 60 percent range. However, this was not true of all centers. Some centers had very good results with conventional therapy, much like the University of Minnesota. In general, the convergence mentioned above was beginning to take shape and it seemed quite clear that cyclosporine alone or in combination with other immunosuppressive agents had gained an upper hand over conventional therapy.

By 1986, at the Helsinki conference, variations among immunosuppressive protocols, including conversion protocols, were an even more significant focus than they were in Minneapolis. It was beginning to appear that people were ready to try anything in terms of combining immunosuppressive agents. Also, while conversion from cyclosporine to conventional therapy was discussed in Minneapolis, further discussion took place in Helsinki. However, the number of observational as opposed to randomized studies appeared to increase. Such studies often raised more questions than they answered.

The results of the trials reported upon in Helsinki are summarized in Table 3-11. As is apparent from this table, not all reports were based on trials involving two or more alternative immunosuppressive protocols. Many of the studies involved but a single protocol. Nonetheless, as is apparent, protocols including cyclosporine had much higher graft survival rates associated with them. Also, it was at Helsinki that triple and quadruple protocols began to emerge in their own right.

Table 3-10
Summary of Graft Survival Rates for Kidney Transplant Recipients as Presented at the Tenth International Congress of the Transplantation Society, Minneapolis, Minnesota, 1984

Author	Location	Study Design	Immunosuppressive Protocols	Overall 1 Year Graft Survival
Hourmant, *et al.*, 1985:1158	Nantes, France	RCT(c)	AZA+PRED+ATG	73%
			CSA+AZA+PRED+ATG	92%
			CSA+PRED	88%
Wood, *et al.*, 1985:1164	Oxford, England	RCT(c)	CSA	71%
			AZA+PRED	61%
Canafax, *et al.*, 1985:1176	Minneapolis, Minnesota	RCT(c)	AZA+PRED	82%
			CSA+AZA+PRED	88%
			CSA+PRED	82%
Illner, *et al.*, 1985:1181	Munich, West Germany	OBS	CSA+AZA+PRED	70%
			AZA+PRED	50%
Johnson, *et al.*, 1985:1197	Manchester, England	RCT	AZA+PRED	66%
			CSA	80.2%
			CSA+PRED	78.6%
Halloran, *et al.*, 1985:1201	Canadian Multicentre	RCT	AZA+PRED+ALG	84%
			CSA	78%
Squifflet, *et al.*, 1985:1212	Brussels, Belgium	RCT	CSA+PRED	88%
			AZA+PRED+ALG	100%
			AZA+PRED+ATG	60%
			AZA+PRED	83%
Fries, *et al.*, 1985:1231	Villejuif-Cedex, France	OBS	CSA+AZA+PRED	83.5%
			AZA+PRED	84%
Henry, *et al.*, 1985:1244	Columbus, Ohio	OBS	AZA+PRED+ALG	78%
			CSA+PRED	87%

(c) = trial involves a conversion protocol.

RCT = randomized control trial
OBS = observational study

Table 3-11
Summary of Graft Survival Rates for Kidney Transplant Recipients as Presented at the Eleventh International Congress of the Transplantation Society, Helsinki, Finland, 1986

Author	Location	Study Design	Immunosuppressive Protocols	Overall 1 Year Graft Survival
Henny et al., 1987:1853	Leiden, Netherlands	RCT	AZA+PRED	66%
			CSA+PRED	87%
MacDonald et al., 1987:1865	Canadian Multicentre	RCT	CSA+PLACEBO	88%
			CSA+PRED	78%
Gianello et al., 1987:1867	Brussels, Belgium	RCT	CSA+PRED	84.4%
			AZA+PRED	81.5%
Fries et al., 1987:1911	Villejuif, France	RCT	AZA+PRED+ALG	76%
			CSA+AZA+PRED	83%
Deierhoi et al., 1987:1917	Madison, Wisconsin	OBS	CSA+AZA+PRED+ALG	85% (2-Yrs.)
Henry et al., 1987:1920	Columbus, Ohio	OBS	CSA+AZA+PRED	97%
Jones et al., 1987:1926	Oxford, England	OBS	CSA+AZA+PRED	79%
Light et al., 1987:1927	Washington, D.C.	OBS	CSA+AZA+PRED+ATGAM	91%
Halloran et al., 1987:1931	Toronto, Ontario	OBS	CSA+AZA+PRED+ALG	84.5%
DeVecchi et al., 1987:1933	Milan, Italy	RCT	CSA+MP	90%
			CSA+AZA+MP	92%
Salaman et al., 1987:1935	Cardiff, Wales	RCT	CSA	78%
			CSA+AZA+PRED	75%
Schweizer et al., 1987:1944	Hartford, Connecticut	OBS	CSA+AZA+PRED	95%
Canafax et al., 1987:1947	Minneapolis, Minnesota	RCT	CSA+PRED (CAD)	82%
			AZA+PRED+ALG (CAD)	73%
			CSA+AZA+PRED+ALG (CAD)	88%
Lundgren et al., 1987:2074	Scandanavia	RCT	CSA+PRED	80%
			CSA(LO)+AZA+PRED	80%
			CSA(HI)+PRED	73%

RCT = randomized control trial
OBS = observational study

Interestingly, at the Pittsburgh conference honoring Dr. Starzl, virtually no paper was presented that compared cadaveric kidney transplant recipient graft survival rates according to immunosuppressive protocol. Two papers from Japan looked at different immunosuppressive protocols; however, one of them failed to report survival data (Uchida et al., 1988:401) and the other involved living related donor transplants (Marumo et al., 1988:406). Thus, based on this, we can conclude that the issues surrounding alternative immunosuppressive protocols were rather uninteresting, or they were simply too mundane, since the intent of the Pittsburgh conference was to serve as a forum for new and original work that was being presented for the first time. Obviously, reports of ongoing clinical trials would hardly qualify on the latter grounds.

To provide still further perspective on cyclosporine trials, we have prepared Table 3-12 which summarizes the results of numerous other studies that have been published since 1985. These papers did not appear in any of the proceedings of the foregoing meetings. They do, however, add to our general stock of knowledge regarding the administration of cyclosporine in renal transplantation.

Finally, at the Second International Congress on Cyclosporine, held in November 1987, numerous papers were presented on various cyclosporine protocols (Kahan, 1988:2; Keown, 1988:1). The trend here was interesting, however. Very few papers presented results based on what has been traditionally referred to as conventional therapy or, if they did, conventional therapy was offered as an arm of a trial involving conversion therapy. In short, there are very few ongoing current trials comparing conventional

Table 3-12
Miscellaneous Reports on Graft Survival Rates Associated With Various Immunosuppressive Protocols

Author	Location	Study Design	Immunosuppressive Protocols	Overall 1 Year Graft Survival
Barry *et al.*, 1986:125	Portland, OR	OBS	CSA+PRED	81.1%
			CSA+AZA+PRED	100%
Kahan *et al.*, 1983:2469	Houston, TX		CSA+PRED	81%
			AZA+PRED	51%
Opelz *et al.*, 1985:1015	Europe North America, Others	OBS	CSA +?	74%
			AZA+PRED	62%
Hull *et al.*, 1986:128	Dallas, TX	OBS	CSA+AZA+PRED	81%
First *et al.*, 1986:132	Cincinnati, OH	OBS	CSA+AZA+PRED	82%
Feduska, *et al.*, 1986:136	San Francisco, CA	OBS	CSA+PRED	82%
			AZA+PRED	55%
Tilney *et al.*, 1986:179	Boston, MA	OBS	CSA+PRED	71%
Gordon *et al.*, 1987:44	Pittsburgh, PA	OBS	CSA+PRED	79.4%
Deierhoi *et al.*, 1987:71	Madison, WI	OBS	CSA+AZA+PRED+ALG	87%
DeVecchi *et al.*, 1987:198	Milan, Italy	OBS	CSA	96%
			CSA+METHYLPREDNISOLONE	78%
Lundgren *et al.*, 1986:66	Scandanavia	OBS	CSA+PRED(LOW DOSE) (HLA MATCHING, TRANSFUSIONS)	68%
Persson *et al.*, 1987:3586	Scandanavia	OBS	CSA(Moderate)+PRED	77.1%
			CSA(Low)+AZA+PRED	79.7%
Mourad *et al.*, 1987:3672	Montpellier, France	RCT	AZA+PRED+ALG	83%
			CSA+AZA+PRED	91%
Grino *et al.*, 1987:3674	Barcelona, Spain	OBS	CSA+PRED+ALG	100%*
			CSA+PRED	96%
Griffin *et al.*, 1987:3685	Cardiff, UK	RCT	CSA+AZA+PRED	85%
			CSA+AZA	
			CSA	86%
			CSA	

*6-month survival rates.

therapy with cyclosporine therapy. If such comparisons are made, they usually are based on historical data for conventional patients. At any rate, the papers presented in Washington, D.C. are summarized in Table 3-13. Clearly, the trends apparent from the early tables continue to exist, as indicated in Table 3-13. While the majority of the studies involved cyclosporine and prednisone, some still used cyclosporine monotherapy and several involved triple drug therapy. Finally, as shown, several included a conversion protocol.

Interpreting the results of the foregoing tables is not a straightforward exercise. Each of the various trials/investigations vary considerably, so much so that it is difficult to draw any direct inferences. For example, protocols, although containing the same pharmacological agents, may differ in their administration schedule. Also, procedures for transplant recipient preparation vary across trials. In short, the assessments contained in the preceding tables are very crude. Nevertheless, one gets the sense that one-year graft survival rates have improved still further for cyclosporine-treated patients, with some centers reporting one-year survival rates in excess of 90 percent (Kahan, 1988:1). It is also apparent that graft and patient survival rates are beginning to further converge, much as they did in the early days of transplantation. The points of convergence, however, are far different between the two periods in the history of renal transplantation.

Side Effects and Complications Associated with Immunosuppressive Agents

Immunosuppressive therapy is an imperfect science--at best it is an ill-understood art. Virtually every available immunosuppressive agent has

Table 3-13
Summary of Graft Survival Rates for Renal Transplant Recipients as Presented at the Second International Congress On Cyclosporine, November, 1987

Author	Location	Study Design	Immunosuppressive Protocols	Overall 1 Year Graft Survival
Land *et al.*, 1988:73	Europe	RCT	AZA+PRED CSA	52% 72%
Jain *et al.*, 1988:82	Halifax Nova Scotia	OBS	CSA+PRED	77.9%
Xie *et al.*, 1988:99	Shanghai, China	OBS	CSA+PRED AZA+PRED	77% 50%
Feduska *et al.*, 1988:102	San Francisco, CA	OBS	CSA+PRED	79% 50%
Salaman, 1988:117	Cardiff, Wales	RCT	CSA CSA+AZA+PRED	80% 76%
Fries *et al.*, 1988:130	Kremin-Bicetre France	RCT	AZA+PRED CSA+AZA+PRED	78.1% 81%
Koote *et al.*, 1988:136	Leiden, The Netherlands	RCT	CSA(Hi)+PRED CSA(Lo)+AZA+PRED	NR/NS NR/NS
Abbud-Filho, *et al.*, 1988:164	Sao Paulo, Brazil	RCT(c)	CSA+PRED AZA+PRED	90% 74%
Spielberger, *et al.*, 1988:169	Innsbruck, Austria	RCT(c)	CSA AZA+PRED	86.2%* 91%

OBS = observational study (not randomized)
RCT = randomized controlled trial
(c) = trial involves a conversion protocol

*At 4 years with 3 months posttransplant as starting point.

attendant side-effects. While many of these may be minimized, their long-term consequences are unclear. As transplant recipients survive for increasingly long periods of time, in larger numbers, the untoward effects of these agents will hopefully be clarified.

We will now somewhat briefly consider the side-effects and complications associated with various immunosuppressive agents. Because it has come to dominate the field of transplantation, primary attention will focus on problems attendant to the administration of cyclosporine. As with all immunosuppressive drugs, the various side-effects and complications associated with cyclosporine can be characterized as short-term and long-term. Obviously, given the relatively short time over which cyclosporine has been available for clinical use, many of the complications now recognized are of a short-term nature, although the initial experience with lymphomas was disconcerting.

Of the major immunosuppressive agents, perhaps azathioprine is believed to be the safest. The major side-effect is bone marrow depression. Steroids, however, have a rather large number of dose-related problems associated with their use, making long-term administration undesirable (Kjellstrand, 1975:123). These include: hypertension, obesity, diabetes, vision disorders, Cushinghoid signs, and ischemic bone necrosis. The major problems associated with cyclosporine are primarily dose-related, as well. These include, first and foremost, nephrotoxicity (Myers et al., 1984:699). In addition, patients may experience, hypertension, hepatotoxicity, malignancy, various neurological complications, hirsutism, and gum hyperplasia. Because of their dose-related nature, many of these problems are amenable to change through dose-reduction. However, because multiple immunosuppressive agents are currently in use, increasing the steroid dose while reducing the cyclosporine dose may give rise to steroid-induced side-effects. Thus, as is well-recognized, the appropriate administration of immunosuppressive agents is a difficult balancing act encumbent upon clinicians responsible for the care of the patient.

Despite its inherent difficulties, most would agree that the advantages of cyclosporine are considerable. In addition to the substantially increased graft survival rates described above, patients on cyclosporine therapy, when compared with patients on conventional therapy, tend to have a reduced frequency of rejection episodes, reduced requirements for steroids, and reduced morbidity (Pichlmayer et al., 1985:6). More specifically, cyclosporine has the following features: (1) high immunosuppressive potency, (2) selectivity for T-lymphocytes, (3) no bone marrow toxicity, and (4) the effect on the immune system can be quickly reversed. The major problem associated with cyclosporine--nephrotoxicity--can be displayed differentially and is more or less amenable to immunologic manipulation depending upon the distinct form it takes--early postoperative nephrotoxicity, the acute nephrotoxic episode, and chronic nephrotoxicity. Chronic nephrotoxicity, if it can be altered, can usually only be done with agents other than cyclosporine. This, of course, is a primary indication for conversion therapy.

Now let us focus our attention on the short-term complications associated with the administration of cyclosporine. While numerous reports have appeared in the literature documenting these, we have chosen to first report the results of the major clinical trials comparing conventional therapy with cyclosporine therapy.

In an early report by Najarian and his colleagues (1983:438), the data showed that only 12 of 70 patients (17%) experienced rejection eposides, whereas 36 of 67 conventionally treated patients did so (54%). Their results also showed that cyclosporine patients had fewer multiple rejection episodes despite the fact that the corticosteroid dose for these patients was one-half that of conventionally-treated patients.

Najarian also reported a much lower rate of infection among patients treated with cyclosporine and prednisone than those on conventional therapy (Najarian et al., 1983:438; Peterson et al., 1983:457). Only 2 of 70 cyclosporine-treated patients developed overt cytomegalovirus (CMV) disease (3%). During the same period, however, their analyses revealed that 22 of 67 conventionally-treated patients developed CMV (33%). In six cases the CMV was lethal. In addition, Najarian et al. reported that there was less than 50 percent incidence of bacterial, fungal, and non-CMV viral infection in the cyclosporine-treated patients.

To be sure, the foregoing results represent the early experience at the University of Minnesota. More recently, Sutherland et al. (1985:318) continue to report that patients receiving cyclosporine and prednisone have significantly fewer rejection episodes, infection episodes, and number of days spent in hospital than do patients receiving azathioprine, prednisone, and antilymphocyte globulin (ALG).

The Pittsburgh group also noted early that the rate of infectious episodes was much lower among cyclosporine patients than those treated conventionally (Hakala et al., 1983:465). A comparison of the infection rates between the two groups showed a rate twice as high for patients on conventional therapy. In addition, the authors reported that most infectious episodes encountered among cyclosporine patients were less serious.

Initial results from the Canadian Multicentre Trial also showed some differences in the rate of infection among patients on cyclosporine and those receiving conventional therapy. CMV infections were substantially less of a problem among cyclosporine patients, but other infections were not so startlingly different. Moreover, probably none of the differences in infection episodes presented in Table 3-14 are statistically significant.

A more recent report from the Canadian Multicentre Transplant Study Group (1986:1219), based on an analysis of 291 renal transplant recipients, revealed that CMV infections, other viral infections, and pneumonias were somewhat more frequent among patients on conventional (control) therapy (see Table 3-15). Other viral infections included herpes (cyclosporine, 21; control, 28), warts (cyclosporine, 5; control, 3), chicken pox and shingles (cyclosporine, 2; control, 1), hepatitis B (control, 1), and unknown infections (cyclosporine, 1; control 3). The investigators report these data to "... indicate that infections were not more frequent among patients in cyclosporine therapy than among controls."

The 1983 report from the European Multicentre Trial Group, unlike the foregoing reports, indicated that there was no difference in the frequency of bacterial, viral, or fungal infections between the cyclosporine-treated and the conventional therapy groups. No effort was made to explain why differences were not found, given the results of other major clinical trials.

Based on the foregoing initial and followup reports, it is reasonable to conclude that cyclosporine has had a positive impact on the infectious, largely short-term complications, attendant to renal transplantation.

Table 3-14
Infectious Complications Among Renal Transplant Patients on Conventional Therapy and Cyclosporine

Complication	Conventional Treatment	Cyclosporine Treatment
	(Number of Complications)	
Septicemia	8	4
Abscesses	7	2
Systemic fungal infection	2	1
Local fungal infection (candidiasis)	10	8
Cytomegalovirus	9	2
Other viral infection	18	16
Urinary tract infections	26	32
Wound and skin infections	10	9
Pneumonia	6	6
Other	3	1

SOURCE: Canadian Multicentre Transplant Study Group, 1983: 809. Also see Laupacis and the Canadian Transplant Study Group, 1983:2748.

Table 3-15

Infectious Complications Among Renal Transplant Recipients in the Canadian Multicentre Trial at Three-Years' Followup

Complication	Cyclosporine	Control
Septicemia	10	11
Abscesses	11	7
Systemic fungal infection	2	3
Cytomegalovirus	6	11
Other viral infection	29	36
Urinary tract infection	48	45
Local candidiasis	17	20
Wound and skin infection	16	19
Pneumonia	15	20
Other infection	18	17

SOURCE: Canadian Multicentre Study Group, 1986:1224

While this positive gain is important, it will be necessary to carefully evaluate forthcoming changes that are likely with triple- and quadruple-drug immunosuppressive protocols. In an effort to avoid nephrotoxicity, larger doses of a wide array of immunosuppressive agents are being used. These may lead to a different frequency and mix of infectious disorders. On the positive side, however, the long-standing experience of the University of Minnesota with multiple drug and technique immunosuppression suggests that cyclosporine-treated patients are likely to continue to have a positive infectious disease experience.

The side-effects associated with cyclosporine therapy, as noted previously, have been the subject of relatively little attention, although some rather systematic studies have been conducted. In some areas, such as malignancies, the evidence amassed thus far is considerable. While it is impossible to review the contents of all published studies, we will, once again, begin with a brief consideration of the early reports on the side-effects that appeared to be associated with cyclosporine. We will then look at the evidence with regards to cancer, and then close with a review of several recent reports on long-term survivors of renal transplants. These studies shall provide a baseline against which long-term cyclosporine therapy will eventually be evaluated.

As already noted, the major problems attributed to cyclosporine therapy are nephrotoxicity, hepatotoxicity, hirsutism, tremors, central nervous system toxicity (including seizures), gingival hyperplasia, hypertension, hemolytic anemia, thrombocytopenia, lymphoma, and lymphoproliferative disorders. It is important to underscore the fact that many of these side-effects can be reversed through a reduction in cyclosporine dose.

In its early reports, the Minnesota group indicated that the only side effects it observed were fine hair growth, a fine tremor of the upper extremity, a desquamous rash in two patients, and one patient with a fibroadenoma of the breast. Only three patients were observed with hepatotoxicity. Nephrotoxicity was the most significant complication. The investigators noted that only one-third of the patients had normal renal function three to four months posttransplant (Najarian et al., 1983:438).

The Pittsburgh group initially reported few side effects associated with cyclosporine--nephrotoxicity being foremost. They reported seeing two malignancies including one bowel lymphoma that was rejected and a Kaposi's sarcoma that resolved spontaneously on reduced cyclosporine dose. Hakala et al. (1983:465) underscored the fact that they were seeing fewer cataracts, decreased Cushingoid appearance and fewer bone problems among patients on cyclosporine. These, of course, are all problems often experienced by patients on conventional immunosuppressive therapy.

The Pittsburgh group has recently reported on their long-term results of cyclosporine steroid therapy for 131 nonmatched cadaveric renal transplants (Gordon et al., 1987:44). They briefly comment on their experience with malignancy. Two lymphomas were diagnosed and treated with local resection and reduction of immunosuppression. Neither lymphoma had recurred at 51 and 66 months. A third similar lesion was an incidental finding in a patient who died of pneumonitis. Another patient in the series has reportedly been living for more than four years in symbiosis with a disseminated Kaposi's sarcoma which "waxes and wanes" with cyclosporine dose. Two carcinomas were diagnosed in males with excellent graft function. One patient had widespread metastases from an unknown primary 71 months after transplantation. The other patient developed a larcrimal duct cancer three-years after transplantation which was controlled by radiotherapy, and then committed suicide when a separate oropharyngeal carcinoma developed after four-years.

The first major report from the Canadian Multicentre Trial Group also documented posttransplant complications. They noted that three patients on cyclosporine died, while eleven patients on conventional therapy did so. Two patients in the cyclosporine group developed cancer, while no cases of cancer were seen in the conventional therapy group. Aside from nephrotoxicity, the frequency of noninfectious complications was similar in both groups, except for the incidence of renal-artery thrombosis or stenosis which developed in seven cyclosporine-treated patients and one on conventional therapy. Twelve patients on conventional therapy developed severe leukopenia, but only one patient on cyclosporine did so. The frequency of other noninfectious complications is provided in Table 3-16.

In their followup report, the Canadian Multicentre Study Group provides fewer data on the complications of the patients at three-years' posttransplant. They note that vascular complications, hematologic complications, neurologic problems (seizures and tremors), gastrointestinal complications, hypertrichosis, and gingival hyperplasia appeared to be increased among the patients on cyclosporine therapy. Also, four cases of cancer were reported in the cyclosporine group, as compared with two in the control group. Of the four cases in the cyclosporine group, two cases were confirmed as lymphomas, one case was diagnosed as a lymphoma by biopsy but not confirmed in terms of clinical course, and one case was confirmed as skin cancer in situ.

Table 3-16
Noninfectious Complications Among Renal Transplant Patients on Conventional Therapy and Cyclosporine in The Canadian Multicentre Study Based on Initial Experience

Complication	Conventional Treatment (Number of complications)	Cyclosporine Treatment (Number of complications)
Urinary leak	4	6
Renal bleeding	8	5
Hydrocele or lymphocele	5	3
Renal artery thrombosis or stenosis	1	7
Systemic vascular complication	3	6
Hypertension	32	42
Cancer	0	2
Asceptic necrosis	3	1
Other musculoskeletal complication	3	3
Severe leukopenia	12	1
Seizures	3	4
Major neurologic complications	0	3
Minor neurologic complications	1	12
Psychiatric complications	4	3
Gastrointestinal hemorrhage	6	3
Other gastrointestinal complications	2	6
Steroid-induced diabetes	5	2
Clinical liver toxicity	4	4
Hirsutism	1	30
Gum hyperplasia	0	7
Cushingoid signs	19	17
Acne	18	13

SOURCE: Canadian Multicentre Transplant Study Group, 1983:809.

Complications that tended to occur more frequently in the control group included severe leukopenia and steroid-induced diabetes.

The frequency of side-effects between the initial and follow-up reports of the European Multicentre Trial (1982:57; 1983:986) remained unchanged. The most common side effects (with their frequency) in cyclosporine patients were: hirsutism (44%), fine tremor (39%), gingival hypertrophy (28%), anorexia and nausea (21%), and hyperaesthesia of the hands (11%). Again, in the European Trial these side effects were reversed with dosage reduction. Two cyclosporine patients developed benign breast lumps and one a squamous cell carcinoma of the right cheek.

As expected, patients on conventional therapy were not free of complications. The most common side effect was Cushingoid appearance (54%). Fourteen patients (12%) had bone marrow depression, which in nine patients required cessation of azathioprine. There were four cases of gastric and duodenal ulceration, two requiring surgery. Three patients developed moderate or severe diabetes. One patient developed a basal-cell carcinoma of the right temporal area.

The Cambridge group, in their major summary report (Merion et al., 1984:148) on 79 recipients of cadaveric renal allografts who were treated with cyclosporine as the sole immunosuppressive agent and 29 concurrent transplant recipients treated with conventional immunosuppressants, found that nephrotoxicity was a problem for ten patients receiving cyclosporine, but that these patients responded well when the dose of cyclosporine was lowered. They also report that among patients discharged with functioning grafts, the mean serum creatinine level in the cyclosporine group at discharge was not significantly higher than in the conventionally treated group. Finally, the

Cambridge group noted that with increased experience with cyclosporine, the lymphomas among cyclosporine patients would likely decrease.

Although many investigators have commented upon the development of lymphomas and cancer in transplant recipients, Penn is generally recognized as the authority on the matter. This is primarily due to the fact that Penn maintains the Cincinnati (formerly Denver) Transplant Tumor Registry (CTTR).

In 1983, Penn reported that he had received data on 1767 types of tumors (see Table 3-17) in 1661 organ transplant recipients (Penn, 1983:2790). Of these, 1622 patients received a kidney, 33 received a heart, 4 received bone marrow, and two received liver transplants. Penn reported that lymphomas made up a disproportionately high percentage of neoplasms in these patients. In the general population, he noted, they comprise 3-4 percent of all malignancies. In contrast, they made up 314 of 1767 neoplasms (18%) seen in the transplant patient population. Moreover, he suggests that their true incidence is higher, if we exclude nonmelanoma skin cancers and in situ carcinomas of the cervix and of the uterus which are omitted from most cancer statistical analyses. Having done this, the actual percentage rises to 26 percent, making lymphomas the most important group of tumors seen in transplant recipients.

In the 313 patients with lymphomas, Penn reports that prednisone was given to 302 (96%), azathioprine in 281 (90%), antilymphocyte globulin (ALG) in 105 (34%), local radiation of the graft in 95 (30%), splenectomy in 61 (19%), actinomycin in 41 (13%), cyclophosphamide in 18 (6%), and cyclosporine in 17 (5%), and miscellaneous other immunosuppressive treatments were used in 24 recipients. Based on these results, Penn (1983:2796) concluded that "... it appears that the increased incidence of

Table 3-17
De Novo Malignancies in Organ Allograft Recipients as Reported by Penn, 1983

Type of Cancer	Number of Patients*
Cancers of the skin and lips	674
Solid lymphomas	314
Reticulum cell sarcomas	155**
Kaposi's sarcomas	60**
Unclassified lymphomas	42
B-cell lymphomas	26
Hodgkin's disease	10
Lymphosarcomas	8
Plasma cell lymphomas	6
Burkitt's lymphoma	1
Histiocytic medullary reticulosis	1
Mycosis fungoides	1
Carcinomas of uterus	
Cervix (111); body (12)	123
Carcinomas of the lung	86
Carcinomas of colon and rectum	66
Carcinomas of breast	55
Leukemias	45
Carcinomas of vulva and perineum (including scrotum, penis, and anus)	40
Miscellaneous	364
TOTAL	1767

*There were 1661 patients of whom 106 had more than one type of tumor.

**One patient had Kaposi's sarcoma and a reticulum cell sarcoma.

SOURCE: Penn, 1983:2790.

cancers, and particularly lymphomas, cannot be blamed on any single immunosuppressive agent but, rather, it is a complication of immunosuppression per se." Even at this early date in the use of cyclosporine, Penn suggested that the incidence of lymphomas in cyclosporine-treated patients was dose-related and he noted that "Long-term follow-up of large numbers of patients treated exclusively with cyclosporine-A will clarify the carcinogenic potential of this agent in man."

Penn (1988:276) has published a more recent paper on cancers subsequent to cyclosporine therapy. This report is based on 3,427 neoplasms that developed in 3,203 patients. He compares 373 neoplasms in 366 cyclosporine-treated patients and 3,054 malignancies in 2,837 recipients of "standard immunosuppressive regimens" (SIR) using azathioprine or, less commonly, cyclophosphamide as the major immunosuppressive agents.

The average time of appearance of tumors after SIR was 64 months (range, 1 to 253 months). After cyclosporine treatment it was only 25 months (range 1 to 233.5 months). Penn notes that several patients at the furthest end of the time spectrum had been switched from SIR to cyclosporine treatment or had received SIR with a first transplant with a subsequent transplant. Only 14 of 366 (4%) were treated exclusively with cyclosporine. The other agents most commonly used were prednisone (345 patients), azathioprine (171 patients), antilymphocyte globulin (99 patients), and OKT-3 (22 patients).

Table 3-18, taken from Penn (1988:276), shows a disproportionately high incidence of lymphomas, Kaposi's sarcoma and renal carcinomas in cyclosporine-treated compared with SIR patients. In addition, there was a

Table 3-18
Comparison Of Tumors After Cyclosporine and Standard
Immunosuppressive Therapy (SIR) as Reported by Penn, 1988

	SIR* (Percent)	CS**(Percent)
Skin cancers	1217 (40)	74 (20)
Lymphomas	352 (12)	111 (30)
Carcinomas of the cervix	172 (6)	6 (2)
Kaposi's Sarcoma	104 (3)	42 (11)
Carcinomas of the vulva/perineum	92 (3)	5 (1)
Carcinomas of the lung	153 (5)	20 (5)
Carcinomas of the colo-rectum	113 (4)	12 (3)
Carcinomas of the breast	103 (3)	13 (3)
Carcinomas of the kidney	86 (3)	21 (6)
Head and neck cancers	86 (3)	7 (2)
Leukemias	78 (3)	2 (<1)
Metastases (unknown primary)	71 (2)	7 (2)
Carcinomas of the urinary bladder	66 (2)	8 (2)
Hepatobiliary carcinomas	54 (2)	4 (1)
Carcinomas of the thyroid	40 (1)	5 (1)
Sarcomas (excluding Kaposi's sarcoma)	38 (1)	5 (1)
Testicular carcinomas	33 (1)	8 (2)
Ovarian cancers	25 (<1)	7 (2)
Miscellaneous neoplasms	171 (6)	16 (4)

*There were 3,054 tumors in 2,837 patients.

**There were 373 tumors in 366 patients.

SOURCE: Penn, 1988:277

lower incidence of skin cancers and uterine cervical carcinomas and carcinomas of the vulva and perineum in the cyclosporine group.

As shown in Table 3-18, lymphomas were the predominant tumors in cyclosporine-treated patients. Penn notes that these tumors appeared in a remarkably short time after transplantation at an average of 12 months (range, 1 to 60 months) compared with an average of 44 months (range, 1 to 196.5) after SIR.

In concluding this report, Penn (1988:276) observes that "With the limited experience gained thus far it appears that the incidence of cancers after the use of cyclosporine is no higher than that of SIR. However, the types of malignancies and their clinical behavior show significant differences between the two forms of therapy." Specifically, the CTTR data shows a disproportionately high incidence of non-Hodgkins lymphoma, Kaposi's sarcoma, and renal carcinomas in cyclosporine-treated patients compared with SIR patients and a lower incidence of skin cancers, _in situ_ uterine cervical carcinomas, and carcinomas of the vulva and perineum.

As of late, numerous reports have begun to appear in the literature concerning the long-term complications of cyclosporine therapy as well as conventional therapy. The results of some of these papers are summarized here as they underscore the complexity of managing the renal transplant recipient over their life course. As one team notes, "Due to the high incidence of serious late-onset complications in kidney graft recipients, we strongly recommend, as others have, that such patients continue to be followed by medical teams with good experience in transplantation" (Toussaint _et al._, 1988:554).

Since October, 1983 the University of Wisconsin transplant program has used the same four-agent sequential immunosuppressive protocol consisting of cyclosporine, azathioprine, prednisone, and Minnesota ALG in 305 consecutive patients (Deierhoi et al., 1987:71). Many commentators have questioned the possibility of over-immunosuppression using this protocol. However, the Wisconsin results suggest that this is not a problem as their experience with serious nonfatal infections is not abnormally high. As shown in Table 3-19, CMV remains the major infectious complication, followed by bacterial sepsis. The investigators found no lymphomas or other malignancies and conclude that "... sequential immunosuppression with CYA, MALG, PRED, and AZA in cadaver renal transplantation provides excellent patient and graft survival and a low risk of infectious complications or malignancy."

Feduska and coworkers (1986:136) at San Francisco, have also reviewed their infectious disease experience for both cyclosporine and conventional therapy. The results are presented in Table 3-20. The most notable differences between the two groups of patients were a higher incidence of septicemia and urinary tract infection among patients treated with conventional drugs.

Sommer and colleagues (1986:69) at Ohio State have reported on infectious complications among mismatched living related donor and cadaveric donor renal transplant recipients (N = 229, 36 = LRD, 193 = CAD) using sequential immunosuppressive therapy. They note that infections were common during the first month posttransplant and primarily consisted of wound infections and oral infections associated with candida or herpes simplex. Their results are shown in Table 3-21. As shown, the incidence of oral herpes simplex infections has surpassed CMV infections as the most

Table 3-19
Incidence of Serious Nonfatal Infections With Quadruple Immunosuppression at the University of Wisconsin

Infection	Number
Cytomegalovirus (CMV)	10
Bacterial Sepsis	5
Pneumocystis	1
Candida wound infection	1
Necrotizing fasciitis	1

SOURCE: Deierhoi *et al.*, 1987:73

Table 3-20
Infectious Disease Complications During the First Year Following Transplantation at the University of California--San Francisco

Complication	Immunosuppressive Protocol	
	CSA+PRED (N=117)	AZA + PRED (N=117)
Septicemia	5	14
Pneumonia	19	15
Systemic fungal infection	0	2
CMV infection	3	1
Wound infection	2	3
Urinary tract infection	38	63
Transplant pyelonephritis	1	1

SOURCE: Feduska *et al.*, 1986:138

Table 3-21

Infections in Recipients at Ohio State University Receiving Sequential ALG-CSA Immunotherapy

	Allograft Type		
Type of Infection*	Living Related (Primary)	Cadaveric (Primary)	Cadaveric (Regraft)
Bacterial			
Pneumonia	1	3	1
Urinary	2	7	2
Wound	1	5	2
Blood	0	1	1
Other	1	9	2
Fungal			
Candida	1	4	2
Aspergillus	0	1	0
Histoplasma	0	0	1
Viral			
Cytomegalovirus	2	6	2
Herpes Simplex	3	12	4
Varicella	0	3	1
Hepatitis B	0	1	0
Epstein-Barr	0	2	0
Total infections	11	54	18
Number of patients involved	9**	41	14
Total Recipients	36	148	39

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*Includes surveillance and clinically directed cultures.

**Some patients had more than one infection.

common infection following renal transplantation even when sequential ALG and cyclosporine was used. Sommer et al. note that recipient death associated with sepsis has been due to CMV in two cases and disseminated histoplasmosis in one instance.

Kahan's group has reported on the long-term results of cyclosporine therapy in mismatched living related donor kidneys (see Flechner et al., 1986:44). They indicate that posttransplant infections were the most common cause of morbidity (total patient N = 86). Of these, the most clinically significant included six viral infections, 21 bacterial infections, and two fungal infections. There were six cases of osteonecrosis of the femoral head, four of which required hip replacement. Three patients required cataract extractions. Two patients were hospitalized with severe acute pancreatitis, and two patients developed upper gastrointestinal bleeding that resolved without surgical intervention. One patient developed a lymphocele that required surgical drainage, and one patient required ureteral reimplantation for a urine leak.

Flechner et al. (1986) also report posttransplant hospitalization experience. Since their initial discharge, 30 patients (35%) have never required readmission to the hospital. Twenty patients required one admission, 18 patients, two admissions, six patients, three admissions, and 12 patients, over three admissions during the 4.5 years of follow-up.

The University of Florida transplant team has also reported on the late results of renal transplantation in a total of 315 primary cadaver and living-related donor transplants performed from 1975 through 1984 (Wynn et al., 1988:329). The complications observed are summarized in Table 3-22. As indicated, most complications occurred early after transplantation,

Table 3-22
Posttransplant Complications Reported by the University of Florida Group

Complication	Prior to Two Years	After Two Years
Bacterial infections	87	31
Pneumonia	12	4
Meningitis	1	0
Urinary tract infection	45	17
Other	29	10
Fungal infections	12	8
Meningitis	1	3
Other	11	5
Viral infections	49	5
Cytomegalovirus	27	1
Herpes simplex	15	0
Varicella zoster	5	2
Epstein-Barr	2	2
Protozoal infections	2	0
Hypertension	94	17
Cataracts	46	6
Steroid-induced diabetes	19	6
Aseptic necrosis	39	16
Chronic liver disease	14	7
Gastrointestinal	40	16
Obesity	15	5
Vascular disease	16	15
Coronary artery disease	4	5
Peripheral vascular disease	11	7
Stroke	1	3
Psychiatric disease	6	3
Neoplastic disease	1	7
Squamous cell	1	4
Other	0	3
Urologic		
Leak	15	0
Obstruction	7	1
Stone	0	2
Other	9	5
Lymphocele	27	1

SOURCE: Wynn _et_ _al_., 1988:329

although the continued occurrence of infections and aseptic necrosis, and the increased number of neoplasms late after transplantation is noteworthy.

Toussaint et al. (1988:554) in their report in the late morbidity of 102 kidney transplants functioning more than five years are quite concerned about long-term complications. They note that myocardial infarction occurred in 12 patients, 39-150 months postoperatively, at 26-62 years. There were also ten episodes of cerebral or subarachnoidal hemorrhage or of cerebral thrombosis in 10 patients. Fatal lung embolism occurred at 81 and 82 months following transplantation in two patients. Another 45 year-old man died of a ruptured atheromatous aneurysm of the thoracic aorta 151 months posttransplant. Malignancies were recorded in 7 of 102 patients under study, occurring 63-204 months following transplantation, at 28-70 years of age. Seven infections were recorded in eleven 22-69 year-old patients and occurred at 60-180 months posttranpslant. Late onset acute rejection was recorded in 6 of 102 patients.

The foregoing summarizes the complications and side-effects associated with immunosuppressive therapy. The account provided here is by no means complete. We have not reviewed every published report on complications and side-effects. This would be a substantial undertaking. What we have done, however, is focus on the major clinical trials conducted thus far. We have reviewed both the early and late results of these trials (Najarian, 1988:5). Based on these and other reports, it is now clear we have entered a new era in renal transplantation, an era in which comparisons are not being made between cyclosporine therapy and conventional therapy, but rather an era within which various multiple drug immunosuppressive protocols are being compared. Many of these protocols include cyclosporine with other agents.

Except in instances where therapeutic conversion is being attempted, virtually no transplant protocol, completely omits cyclosporine, although some induction protocols, such as that of Ohio State University and the University of Wisconsin, may temporarily withhold cyclosporine. This is an area where further study is required, as the therapeutic consequences of many multiple-drug immunosuppressive protocols remain unknown. It is important that we now turn our attention to these protocols in an effort to better understand their goals and what their implications are likely to be.

The Basics of Immunosuppressive Management

Until the clinical introduction of cyclosporine, renal transplant immunosuppressive drug protocols were similar across transplant programs in the United States and abroad. The mainstay therapy consisted of little more than a combination of azathioprine and prednisone, although induction and maintenance protocols varied to some extent. For example, some programs incorporated ALG in their induction protocols and some attempted to modify the immunological response in various other ways using techniques such as those described above. In this regard, some programs such as the University of Minnesota, have routinely performed splenectomies. Nonetheless, not until cyclosporine became available did the variety of protocols followed increase substantially. Not only were a large number of drugs used in combination, but the dose requirements were altered significantly. For example, today low-dose cyclosporine has been incorporated into numerous protocols that involve multiple immunosuppressive agents.

In presenting the various protocols that have been followed, it is important to have a reasonable conceptual understanding of the manner in which immunosuppressive drugs are administered. Land (1987) has suggested, for example, that we distinguish among four different phases in the administration of cyclosporine. These phases can be applied to all immunosuppressive agents and techniques. The phases are as follows: (1) induction treatment, (2) maintenance treatment, (3) chronic renal dysfunction treatment, and (4) anti-rejection treatment.

Induction treatment refers to the initial use of immunosuppressive agents during the immediate, posttransplantation period of about six weeks. It is during this period that the patient's status is most uncertain. Graft function may be unstable, there is almost always coexistent renal injury, and the immune system is in a state of increased alloreactivity.

Maintenance treatment is initiated after graft function has stabilized, when kidney and liver function are normal or subnormal. Infectious complications are absent and alloreactivity has decreased steadily. The maintenance treatment period is often separated into two time frames--before and after 6-months posttransplantation.

Chronic renal dysfunction requires specialized treatment. It is during this time that the use of cyclosporine may create clinical confusion. For example, the problem of distinguishing between a rejection episode and nephrotoxicity is of primary importance. Unfortunately cyclosporine has, in many respects, increased the complexity of transplant recipient management.

Finally, the fourth phase in immunosuppressive treatment is anti-rejection therapy. There is wide variation among transplant teams in their approach to the treatment of rejection. Some teams may simply increase the dose of prednisone, others reinstitute ALG therapy, and, most recently, OKT-3 (Orthoclone) is being used. Obviously, anti-rejection therapy constitutes a short-term phase in the transplant trajectory, although multiple rejection episodes may require the transplant team to re-institute anti-rejection therapy.

For purposes of this discussion, attention will focus on both induction and maintenance immunosuppressive protocols. After a period marked by considerable variation across transplant teams, as noted, immunosuppressive therapy is becoming more uniformly applied. Although therapeutic goals, and therapeutic drug monitoring continue to differ across transplant teams, it is possible to at least examine some commonalities, without case-by-case deviations, as to therapeutic management. Land (1987) has recently accomplished this, in a small publication entitled "Optimal Use of Cyclosporine in Organ Transplantation," printed by Springer-Verlag (Berlin, Heidelberg, Germany). It should be noted that this publication is not widely available in the United States. Various figures taken from this publication are reproduced here with the permission of Sandoz Pharmaceuticals. Also, portions of the text of this monograph have been excerpted, and are reproduced here.

As alluded to above, the use of cyclosporine in combination with steroids and with azathioprine and/or polyclonal and monoclonal antilymphocyte antibodies has become increasingly popular. Thus far it is possible to distinguish among double-drug, triple-drug, and quadruple-drug therapy. Such protocols differ with regards to their posttransplant phases. For example, the initiation and maintenance phases vary across transplant protocols. By reviewing a few such protocols, a general appreciation can be achieved for the types of protocols in use today. This is done by looking at differences in induction therapy and maintenance therapy across protocols.

Immunosuppressive Combination Therapy as Induction Treatment

Double-Drug Induction Treatment--

Double-drug therapy during the induction period, using cyclosporine with steroids, is based upon the concepts that high (= appropriate) doses of cyclosporine are necessary for efficient immunosuppression (by either intravenous or oral route), and that extensive and careful therapeutic drug monitoring in accordance with the proposed therapeutic windows is essential for controlling acute nephrotoxicity as well as later, potentially irreversible, chronic nephrotoxicity, even in cases of severe co-existent renal injury. Both pharmacokinetic and pharmacodynamic studies are useful, particularly during the period immediately after transplantation. This approach is shown diagrammatically in Figure 3-1.

Triple-Drug Induction Treatment--

Triple-drug therapy during the induction period is based on the concept that both acute nephrotoxicity and potentially irreversible, chronic nephrotoxicity in cases with co-existent renal injury can be minimized only by administering low doses of cyclosporine (or even none at all), at least during the period of co-existent renal injury until recovery; and that two other immunosuppressive agents must be added to low dose cyclosporine to avoid the potential risk of under-immunosuppression. Three examples of such approaches are shown in Figure 3-2.

In the simultaneous kidney-function-related therapy approach low doses of cyclosporine are given in combination with azathioprine and prednisone until a serum creatinine value below 3mg percent (265 umol/l) reflects recovery from coexistent renal injury. Azathioprine is then discontinued and

Figure 3-1: Maintenance Treatment: Examples of Different Protocols Using Cyclosporine (CSA) Alone or in Combination with Prednisone (PRED) and/or Azathioprine (AZA)

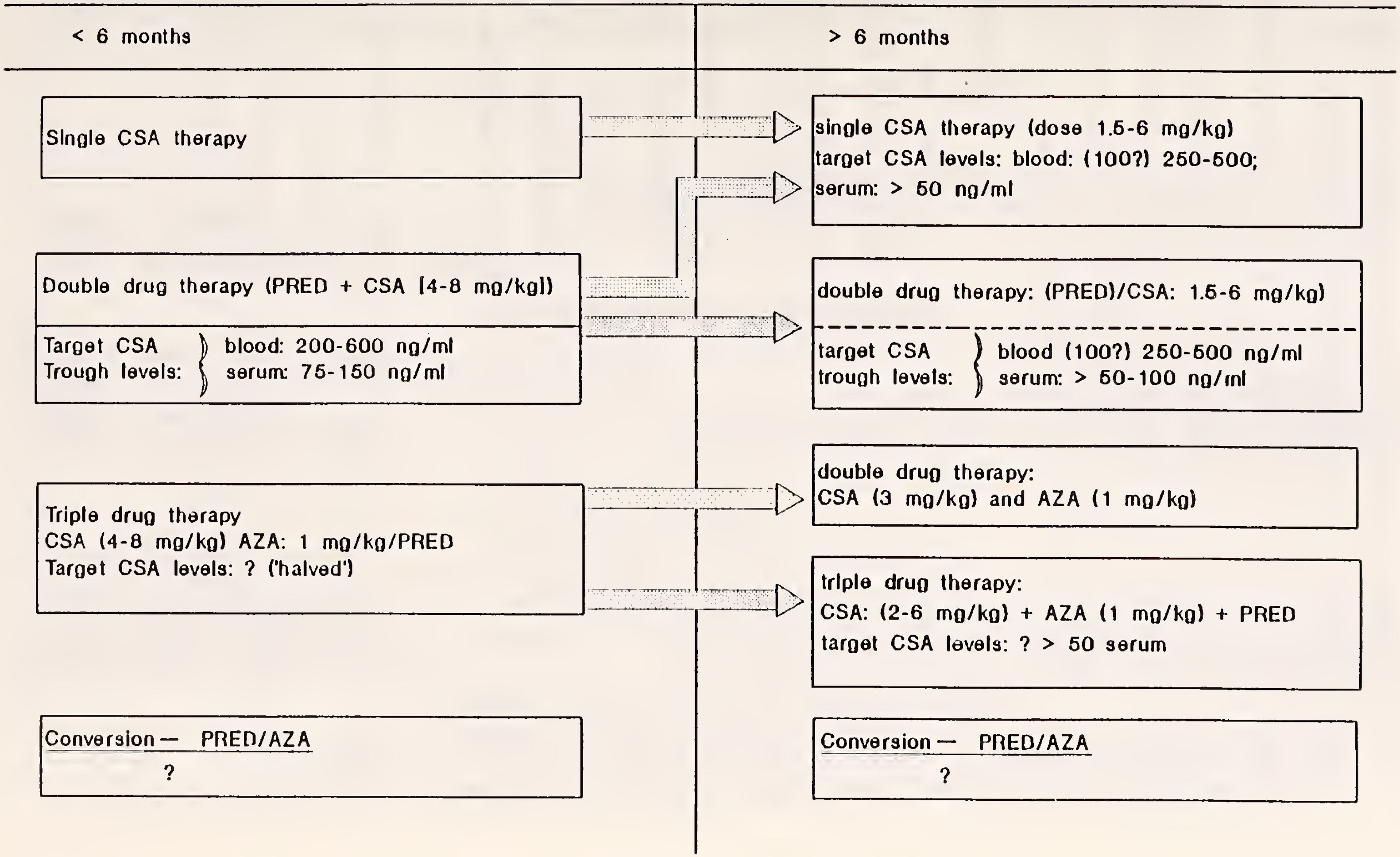
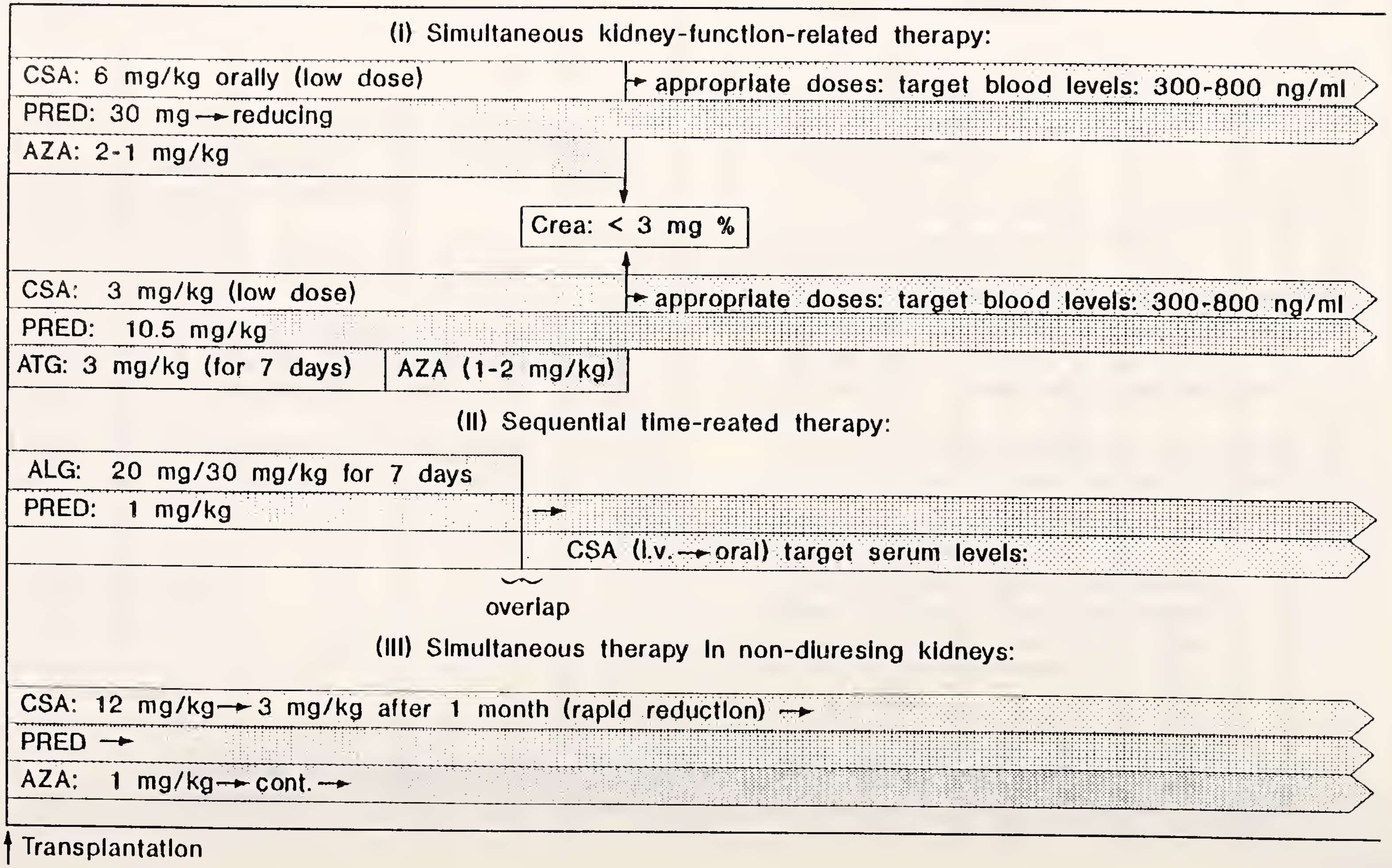

< 6 months
> 6 months
Single CSA therapy
single CSA therapy (dose 1.5-6 mg/kg)
target CSA levels: blood: (100?) 250-500;
serum: > 50 ng/ml
Double drug therapy (PRED + CSA [4-8 mg/kg])
Target CSA Trough levels: blood: 200-600 ng/ml
serum: 75-150 ng/ml
double drug therapy: (PRED)/CSA: 1.5-6 mg/kg)
target CSA trough levels: blood (100?) 250-500 ng/ml
serum: > 50-100 ng/ml
double drug therapy:
CSA (3 mg/kg) and AZA (1 mg/kg)
Triple drug therapy
CSA (4-8 mg/kg) AZA: 1 mg/kg/PRED
Target CSA levels: ? ('halved')
triple drug therapy:
CSA: (2-6 mg/kg) + AZA (1 mg/kg) + PRED
target CSA levels: ? > 50 serum
Conversion — PRED/AZA
?
Conversion — PRED/AZA
?

Figure 3-2: Induction Treatment: Examples of Triple-Drug Therapy Using Combinations of Cyclosporine (CSA), Prednisone (PRED), Azathioprine (AZA), and ALG and ATG


(I) Simultaneous kidney-function-related therapy:
CSA: 6 mg/kg orally (low dose)
→ appropriate doses: target blood levels: 300-800 ng/ml
PRED: 30 mg → reducing
AZA: 2-1 mg/kg
Crea: < 3 mg %
CSA: 3 mg/kg (low dose)
→ appropriate doses: target blood levels: 300-800 ng/ml
PRED: 10.5 mg/kg
ATG: 3 mg/kg (for 7 days)
AZA (1-2 mg/kg)
(II) Sequential time-reated therapy:
ALG: 20 mg/30 mg/kg for 7 days
PRED: 1 mg/kg
→
CSA (i.v. → oral) target serum levels:
overlap
(III) Simultaneous therapy in non-diuresing kidneys:
CSA: 12 mg/kg → 3 mg/kg after 1 month (rapid reduction) →
PRED →
AZA: 1 mg/kg → cont. →
Transplantation

cyclosporine is given at doses appropriate for the desired target levels. Land (1985) and coworkers have used this approach in Munich for over three years. A similar protocol is followed by the Basle group, however, ATG is used instead of azathioprine during the early period (Thiel et al., 1987:25).

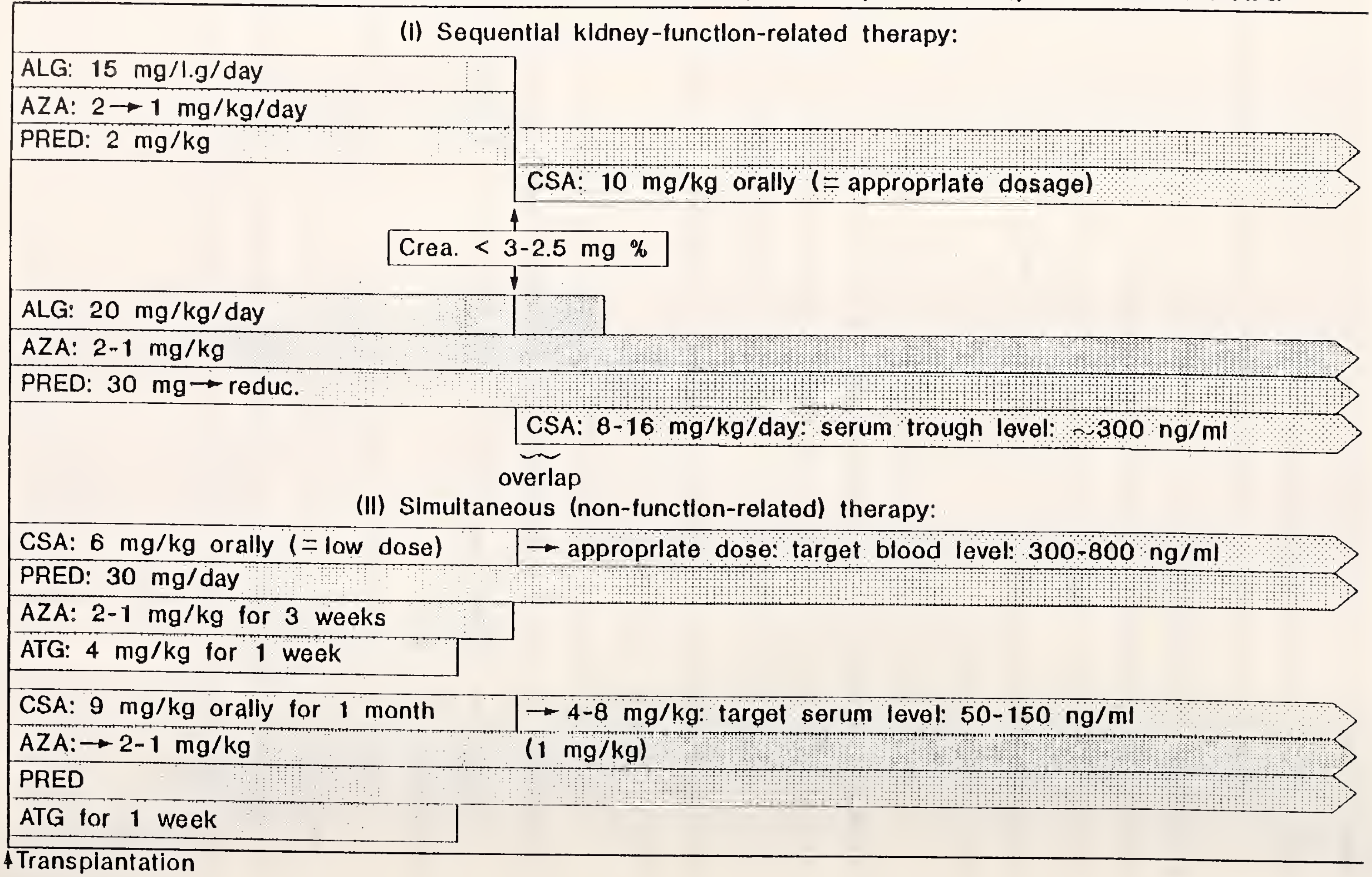
A second approach to triple-drug induction therapy can be described as sequential time-related therapy. The London, Ontario group has used this therapy which begins with the early administration of ALG and prednisone with the ALG later replaced with cyclosporine (see Land, 1987:8). It is noteworthy that this protocol is currently being studied in both heart and liver transplantation.

Finally, a third approach to triple-drug induction treatment is simultaneous "fixed" (= continued) therapy wherein cyclosporine is used in appropriate doses but is rapidly reduced to a dose of 3mg/kg by combining azathioprine and prednisone with cyclosporine. This combination therapy is used by the Portsmouth group, and is predominantly used in non-diuresing kidneys (Slapak et al., 1985:1222; 1985:1355).

Quadruple-drug induction treatment represents a relatively recent innovation. It can be divided into sequential kidney-function-related therapy and simultaneous time-related therapy. These approaches are summarized in Figure 3-3.

The concept underlying the sequential kidney-function-related therapy approach is based on considerations similar to those mentioned from simultaneous kidney-function-related triple-drug therapy, with the exception that instead of low dose cyclosporine, no cyclosporine is used during the

Figure 3-3: Induction Treatment: Examples of Quadruple-Drug Therapy Using Combinations of Cyclosporine (CSA), Prednisone (PRED), Azathioprine (AZA), and ALG and ATG


(I) Sequential kidney-function-related therapy:
ALG: 15 mg/kg/day
AZA: 2→1 mg/kg/day
PRED: 2 mg/kg
CSA: 10 mg/kg orally (= appropriate dosage)
Crea. < 3-2.5 mg %
ALG: 20 mg/kg/day
AZA: 2-1 mg/kg
PRED: 30 mg→reduc.
CSA: 8-16 mg/kg/day: serum trough level: ~300 ng/ml
overlap
(II) Simultaneous (non-function-related) therapy:
CSA: 6 mg/kg orally (= low dose)
→ appropriate dose: target blood level: 300-800 ng/ml
PRED: 30 mg/day
AZA: 2-1 mg/kg for 3 weeks
ATG: 4 mg/kg for 1 week
CSA: 9 mg/kg orally for 1 month
→ 4-8 mg/kg: target serum level: 50-150 ng/ml
AZA: → 2-1 mg/kg
(1 mg/kg)
PRED
ATG for 1 week
Transplantation

immediate postoperative period until there is recovery from coexistent renal injury. Immunosuppressive therapy is started with ALG, azathioprine, and prednisone. When renal function has recovered, either ALG and azathioprine is replaced by cyclosporine or ALG alone is replaced by cyclosporine (see Sommer et al., 1986:69; 1987:85; Sollinger et al., 1986:16).

Simultaneous (nonfunctional)/time-related therapy is being used either in immunologically high-risk patients or in situations such as heart and liver transplantation where rejection is life-threatening.

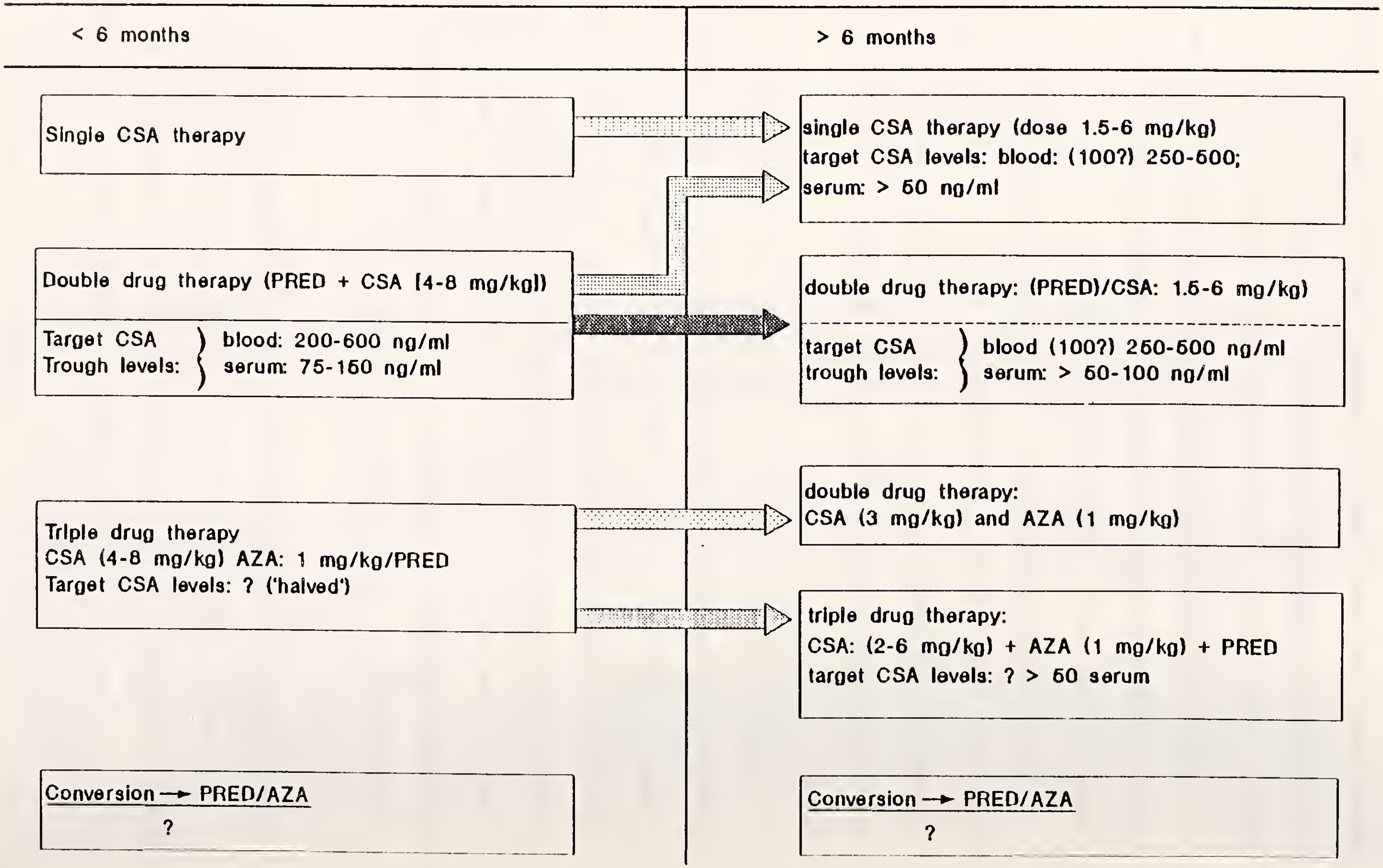
Once again, the concept here is that acute and potentially chronic nephrotoxicity can be efficiently controlled only by administering low doses of cyclosporine but, because of high immunological risk, three further immunosuppressive agents should be added to ensure a safe immunosuppressive index.

Figure 3-3 shows two quadruple-drug protocols where low-dose cyclosporine is combined either with prednisone, azathioprine, and ALG in immunologically high risk recipients of renal transplants (see Land, 1985;1987) or with prednisone, azathioprine, and ATG in heart transplant patients (Land, 1987:10; McGregor et al., 1986:346). In order to avoid over immunosuppression, azathioprine and ATG therapy are limited to three and one weeks respectively in the Munich protocol and that ATG therapy is limited to one week in the Stanford protocol.

Immunosuppressive Combination Therapy as Maintenance Treatment

A variety of protocols for immunosuppressive combination therapy are being widely used during the maintenance period. Figure 3-4 displays several of these approaches. During the period of maintenance treatment, there is a

Figure 3-4: Maintenance Treatment: Examples of Different Protocols Using Cyclosporine (CSA) Alone or in Combination with Prednisone (PRED) and/or Azathioprine (AZA)


< 6 months
> 6 months
Single CSA therapy
single CSA therapy (dose 1.5-6 mg/kg)
target CSA levels: blood: (100?) 250-500;
serum: > 50 ng/ml
Double drug therapy (PRED + CSA [4-8 mg/kg])
Target CSA
Trough levels:
blood: 200-600 ng/ml
serum: 75-150 ng/ml
double drug therapy: (PRED)/CSA: 1.5-6 mg/kg)
target CSA
trough levels:
blood (100?) 250-500 ng/ml
serum: > 50-100 ng/ml
Triple drug therapy
CSA (4-8 mg/kg) AZA: 1 mg/kg/PRED
Target CSA levels: ? ('halved')
double drug therapy:
CSA (3 mg/kg) and AZA (1 mg/kg)
triple drug therapy:
CSA: (2-6 mg/kg) + AZA (1 mg/kg) + PRED
target CSA levels: ? > 50 serum
Conversion → PRED/AZA
?
Conversion → PRED/AZA
?

virtual switch of protocol six months after transplantation, and this change is reflected in the diagram. The protocol after six months is described in greater detail below. In addition to combination regimens, cyclosporine monotherapy is still used in single-drug maintenance treatment as was the case in the European Multicentre Trial (European Multicentre Trial Group, 1983:986).

The concept of single-drug maintenance treatment is based on the assumption that cyclosporine alone used in doses of 1.5 mg/kg to 6 mg/kg does prevent chronic rejection and does not lead to major chronic nephrotoxicity.

It is generally believed that the key prerequisite for cyclosporine monotherapy is careful therapeutic drug monitoring with the aim of keeping the target cyclosporine trough levels in blood/serum within the therapeutic windows.

Double-Drug Maintenance Treatment--

Double-drug maintenance treatment incorporates the use of cyclosporine with prednisone (steroids). There is little doubt that this is currently the most frequently used protocol for cyclosporine administration. Both the evidence and current practice suggests that it is reasonable and desirable to perform routine therapeutic monitoring to adjust the daily dose (1.5-6.0 mg/kg) of cyclosporine to the target cyclosporine trough levels, which should be within the proposed therapeutic windows. The Houston group, under the direction of Kahan, has been among the staunchest of supporters of careful pharmacological monitoring of double-drug maintenance therapy (see Kahan et al., 1987:197). An alternative protocol, proposed by Slapak and colleagues

(1985:1222) at Portsmouth, consists of low-dose cyclosporine administration with azathioprine (1 mg/kg).

Triple-Drug Maintenance Therapy--

The concept of triple-drug maintenance therapy, as used in Minneapolis, Madison, and Columbus, is, as noted previously, based upon the rationale that the side-effects of each drug (particularly the nephrotoxicity of cyclosporine) when administered in low doses are minimal, and that chronic rejection is better controlled by the synergistic--or, rather, additive--effect of all three drugs.

Furthermore, the importance and necessity of pharmacological drug monitoring is lessened. In short, the strict adjustment of the daily cyclosporine dose to target trough levels is viewed to be of limited value. At this time, however, it is noteworthy that the therapeutic windows for cyclosporine through blood/serum concentrations under triple-drug treatment remain undefined. One would expect that they should be lower than the proposed windows for both single- and double-drug therapy.

Conversion Protocols--

Although more extensively discussed below, conversion protocols have been the subject of considerable discussion in the transplantation literature. By conversion, reference is being made to the discontinued use of cyclosporine during the maintenance treatment period. For example, at 3- or 6-months posttransplant, patients may be switched from cyclosporine to alternative conventional immunosuppressive therapy. In other words, cyclosporine is only used during the period of high immunological risk.

Conversion protocols are primarily intended to accomplish the following: (1) minimize cost and (2) reduce potential chronic nephrotoxicity.

Unfortunately, the results of conversion studies are at considerable variance. Some studies, as will be discussed further below, indicate that satisfactory outcomes can be achieved when patients receiving cyclosporine during the maintenance phase are converted to conventional immunosuppressive therapies. Other studies, however, have shown deleterious consequences with graft rejection rates at an uncomfortable level.

Immunosuppressive Therapy for Chronic Renal Dysfunction

Chronic renal dysfunction, as described previously, is a problem often encountered in the administration of cyclosporine therapy. This problem may manifest itself as chronic nephrotoxicity, chronic rejection, or both. There is very little known as to how best to administer cyclosporine during a period when a patient is plagued with one or both of these chronic events. Land (1987:11) has, however, offered a few suggestions.

In the case of chronic nephrotoxicity, Land (1987) indicates that a triple-drug protocol consisting of low or even ultra-low cyclosporine doses in combination with azathioprine and prednisone may be administered initially (see Figure 3-5). If this approach proves unsuccessful, the only alternative is to convert patients to azathioprine and prednisone. However, Land (1987:12) cautions that conversion-induced chronic rejection may occur.

Chronic rejection may also be treated using a triple drug regimen. Initially Land (1987) recommends that the cyclosporine dose should be increased to bring target levels up to 500 ng/ml in combination with azathioprine and prednisone (see Figure 3-6). The latter two agents should

Figure 3-5: Example of Chronic Renal Dysfunction Treatment Using Cyclosporine, Prednisone, and Azathioprine Alone or in Combination (Example: Chronic Nephrotoxicity)

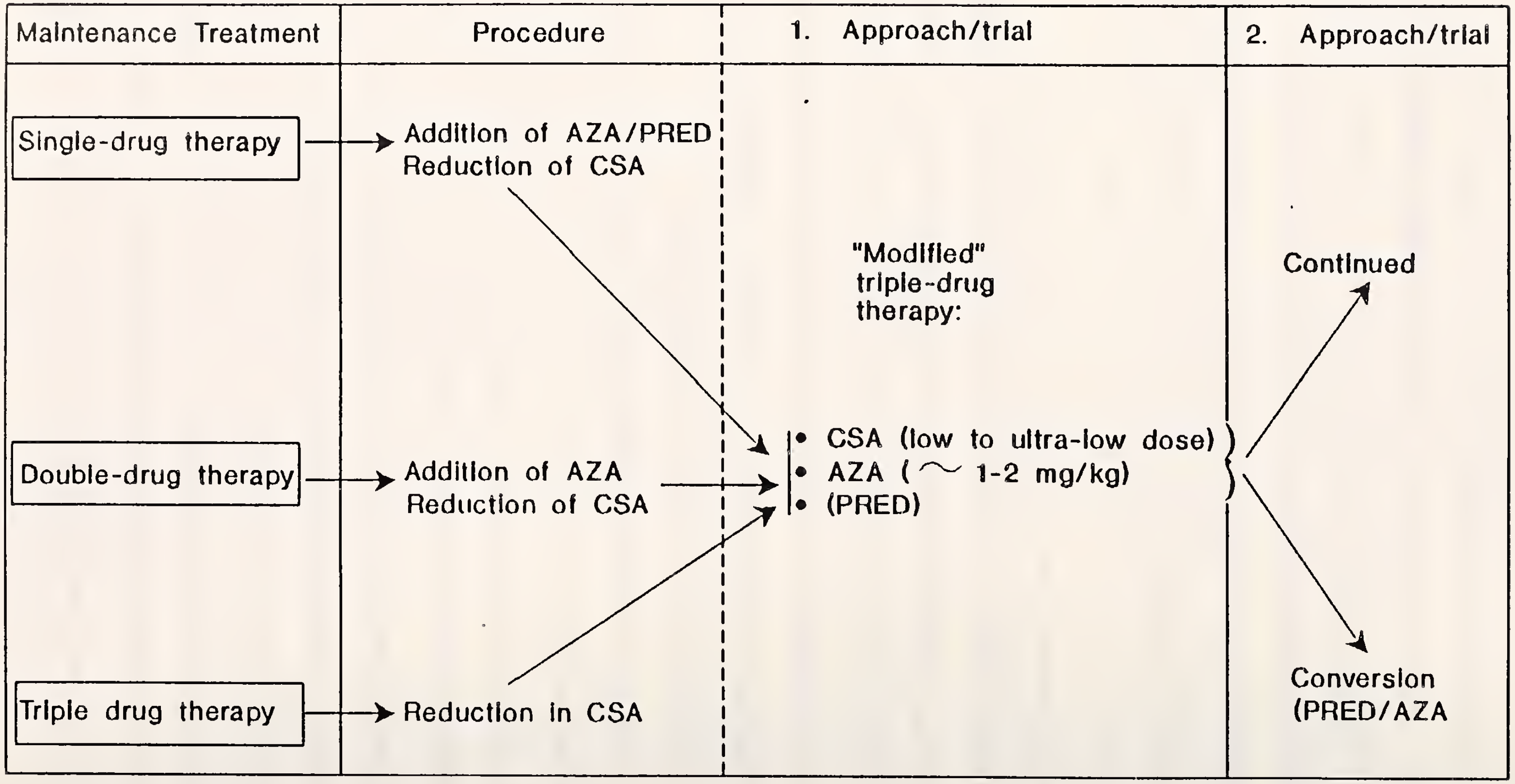
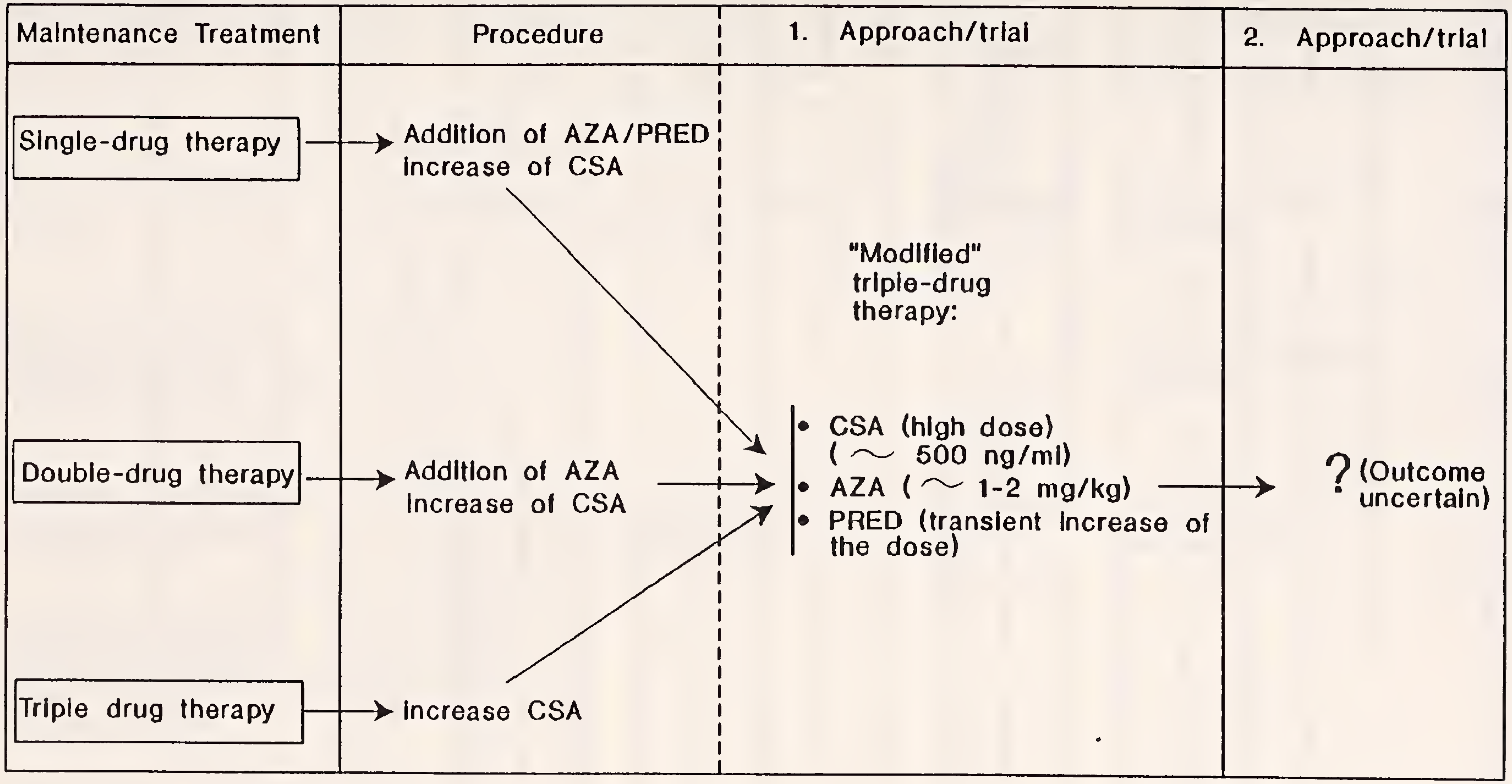


Figure 3-6: Example of Chronic Renal Dysfunction Treatment Using Cyclosporine, alone or in combination with Prednisone, and/or Azathioprine (Example: Chronic rejection)



also be administered with "transiently increased doses." It is noteworthy that only in the exceptional case is a chronic rejection episode reversed, regardless of what attempts are made to rescue the rejecting organ.

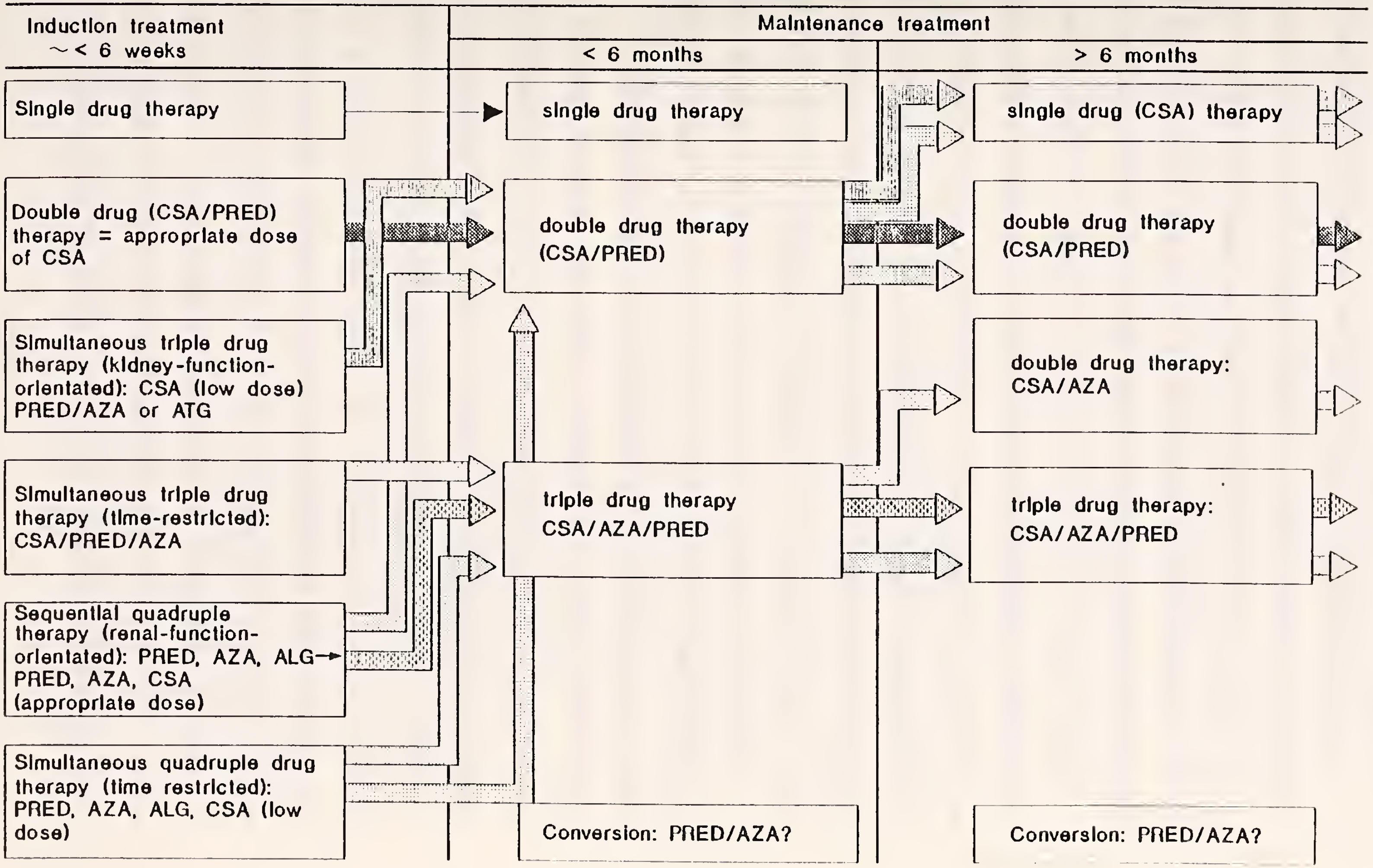
Immunosuppressive Protocols Currently in Use

As described above, numerous immunosuppressive protocols are being used today (Belitsky et al., 1988:78; Boudreax et al., 1987:376; Broyer et al., 1987:3582; Hiesse et al., 1985:1355; Lefrancois et al., 1986:1259; Salaman and Griffin, 1985:1066; Slapak, 1987:958). It is impossible to do justice to each of the protocols followed by various transplant programs throughout the world. The foregoing tables that summarize these protocols are crude at best. They do not include complete descriptions of all the strategies used to induce immunological tolerance. This is not uncommon, however. Even major multicenter studies, such as those of Opelz (1987:641) and Terasaki (1986; 1987; 1988), fail to take into account all the nuances associated with protocols at various transplant centers. The goal here, therefore, is simply to provide the broader picture. If our account is too detailed, we will be unable to see the transplant "forest" for the immunological "trees."

The consistent theme throughout this chapter has been that, regardless of the protocols being followed, overall results have improved and the major untoward consequences of cyclosporine have been brought under control. Land (1987:13) has provided us with a schematic presentation of the protocols currently in use and briefly highlighted the results. His schematic or "pathway" diagram is reproduced here as Figure 3-7.

As Figure 3-7 shows, cyclosporine monotherapy, as pioneered by Calne,

Figure 3-7: Examples of Clinical Use of Cyclosporine (CSA) in Renal Transplantation With Prednisone (PRED), Azathioprine (AZA), Antilymphocyte Globulin (ALG) and Antithymocyte Globulin (ATG)


Induction treatment
~< 6 weeks
Maintenance treatment
< 6 months
> 6 months
Single drug therapy
Double drug (CSA/PRED) therapy = appropriate dose of CSA
Simultaneous triple drug therapy (kidney-function-orientated): CSA (low dose) PRED/AZA or ATG
Simultaneous triple drug therapy (time-restricted): CSA/PRED/AZA
Sequential quadruple therapy (renal-function-orientated): PRED, AZA, ALG→ PRED, AZA, CSA (appropriate dose)
Simultaneous quadruple drug therapy (time restricted): PRED, AZA, ALG, CSA (low dose)
single drug therapy
double drug therapy (CSA/PRED)
triple drug therapy CSA/AZA/PRED
Conversion: PRED/AZA?
single drug (CSA) therapy
double drug therapy (CSA/PRED)
double drug therapy: CSA/AZA
triple drug therapy: CSA/AZA/PRED
Conversion: PRED/AZA?

remains in use at some centers for both induction and maintenance therapy (e.g., Liverpool).

The most commonly used protocol, however, is that pioneered by Starzl--double-drug induction and maintenance therapy--consisting of cyclosporine and prednisone (CSA + PRED). The Houston group also uses this protocol and reports an overall patient survival rate of 97 percent and an overall graft survival rate (including living-related transplants) of 84 percent at one-year.

Both single and double drug protocols require, at least initially, relatively high doses of cyclosporine. Drug maintenance is intense, with or without pharmacokinetic studies. Without such studies, the control of both acute and chronic nephrotoxicity and acute and chronic rejection would be problematic. Land (1987) believes this protocol works very well for living related donor transplants or in patients whose grafts function well initially.

Triple-drug regimens are very popular these days and appear to have enhanced overall results and have reduced some of the posttransplant complications renal transplant recipients have experienced (e.g., nephrotoxicity). To accomplish this, the Munich team has followed an interesting protocol, as described by Land (1987:13). Following coexistent renal injury, cyclosporine is switched to appropriate doses adjusted to desired target trough levels in conjunction with a slightly overlapping stepwise discontinuation of azathioprine. Six months after the transplant a trial of steroid discontinuation is attempted in every patient. In about 75 percent of all patients this trial proves successful. These patients are then maintained on cyclosporine as their sole immunosuppressive agent. In the remaining 25 percent of all patients, Land reports that their creatinine rises slightly after discontinuation, necessitating a re-introduction of steroid treatment.

In addition to the foregoing, Land (1987:13) indicates that the Houston group uses donor-specific hyporesponsiveness as a criterion for prednisone withdrawal during double-drug maintenance treatment (Flechner et al., 1984:685).

The Basle group (Thiel et al., 1987:25) uses a similar protocol starting with triple-drug therapy consisting of 3 mg/kg/day cyclosporine orally, ATG over a period of one week (with subsequent administration of azathioprine if required), and prednisolone. When coexistent renal injury has been resolved (serum creatinine < 3 mg percent, 265 umol/liter, cyclosporine is given in appropriate doses while ATG (or azathioprine) is discontinued. Six months after transplantation, discontinuation of steroids is tried. This is successful in about one-third of the patients. Thiel reports a graft survival rate at one-year of 90 percent. No severe infectious disease has so far been observed.

The Portsmouth group starts with a simultaneous triple-drug regimen consisting of cyclosporine, azathioprine, and prednisone (Slapak et al., 1987:1922). Cyclosporine doses are rapidly decreased to 3 mg/kg/day as maintenance therapy, steroids are discontinued six months after transplantation, and cyclosporine and azathioprine are continued as double-drug maintenance treatment. One-year graft survival rates are in the range of 87 percent.

Both the Ohio State group (Sommer et al., 1986:69) and the Madison group (Sollinger et al., 1986:16) start with sequential quadruple-drug induction treatment. After the patient has recovered from coexistent renal injury, either azathioprine plus ALG (Ohio State) or ALG alone (Madison) is discontinued. With these procedures, maintenance treatment consists of either double-drug or a triple-drug regimen. One-year graft survival rates for both groups are high--85-90 percent. Neither group has reported an incidence of infectious or malignant diseases that is higher than that for previous immunosuppressive protocols. In addition, the incidence of nephrotoxicity during the period of induction treatment was low.

At this point, it is important to consider, in slightly more detail, the immunosuppressive protocols followed by those transplant centers that participated in this study--the University of California, San Francisco, the Ohio State University, the University of Pittsburgh, the University of Texas, Houston, and the University of Wisconsin. This is accomplished in Table 3-23. This table indicates what drugs are administered, and what procedures are performed, at various periods for purposes of immunosuppression. The relevant periods include: preoperative, operative, immediate postoperative, and the long-term maintenance goal. We have also noted the tapering schedule to maintenance goal and the procedures followed to treat a rejection episode. Of course, a reference is cited for the protocol information.

What should be recognized is that variations occur in transplant center protocols over time. For purposes of our study, we did not require centers to follow a standard protocol. In other words, our study is strictly observational. Therefore, deviations are likely to have occurred in intracenter immunosuppressive protocols over the course of this study. These, however, are likely to have been minor variations, and are unlikely to have significantly impacted upon the results of the study.

Table 3-23
Immunosuppressive Protocol by Transplant Center

Preoperative Period	Operative Period	Immediate Post-Operative Period	Tapering to Maintenance Goal	Long-Term Maintenance Goal	Treatment of Rejection	Reference Sources
University of California - San Francisco						
Pretransplant transfusions - Whole blood or packed red blood cells - Groups . 0 transfusions . 1-5 transfusions . 6-10 transfusions .) 10 transfusions	Prednisolone (i.v.) 2 mg/kg Azathioprine (i.v.) 4 mg/kg	Prednisolone (i.v.) 0.5 mg/kg Azathioprine (?) 1.0 mg/kg[1] M-ALG 20.0 mg/kg or ATGAM 15.0 mg/kg	CSA 12.0 mg/kg (discontinue ALG next day)		Prednisolone (i.v.) 7 mg/kg for 3 days with subsequent reduction to oral Prednisone at 2 mg/kg/day and rapid taper If steroid resistant - M-ALG at 20 mg/kg or ATGAM at 15 mg/kg/day	Welzer et al., 1987:61
Ohio State University						
AZA (i.v.) 2 mg/kg Pred (i.v.) 2 mg/kg	Methylprednisolone (i.v.) 500 mg Mannitol (1 to 2 g/kg) Crystalloid (liberal amounts) Packed Cells (liberal amounts) to achieve blood pressure of 140 mmHg or greater and central venous pressure of 15 to 20 cm of water were present	Pred 2 mg/kg/d (1st day) taper every 3rd day by 0.5 mg/kg/d until 9th day AZA continued postop for 5 to 10 days to keep leukocyte count at 3500 cells/mm3 Minnesota ALG 15 mg/kg/d for 5 to 10 days	(THEN) taper to pred dose of 0.3 mg/kg/d by 30th day (THEN) taper to pred dose of 0.25 mg/kg/d for the 60th day (THEN) taper to pred dose of 0.2 mg/kg/d by the 90th day CSA 10 mg/kg/d in single dose once renal function near normal (usually 5-7 days) - Discontinue AZA and ALG			Sommer et al., 1986:69 Ferguson et al., 1987:195

[1] Dose adjusted to maintain a minimum white blood cell count of 400/mm3

Table 3-23 (Continued)
Immunosuppressive Protocol by Transplant Center

Preoperative Period	Operative Period	Immediate Post-Operative Period	Tapering to Maintenance Goal	Long-Term Maintenance Goal	Treatment of Rejection	Reference Sources
University of Pittsburgh						
Pred 17.5 mg/kg Oral CSA	Pred CSA	Pred 200 mg of methylprednisolone or prednisone on day of operation	5-d burst of steroids Pred reduced by 40 mg/d until a daily dose of 20 mg was reached	Pred 20 mg per day CSA weaned to 5 to 6 mg/kg average daily dose at end of 1 year	1 gram bolus of methylprednisolone followed by repeat of the 5-d high dose prednisone	Gordon et al., 1987 Markus et al., 1987:141
University of Texas - Houston						
	CSA (oral) 14mg/kg CSA (IV) 3 mg/kg (loading dose)	CSA (IV) 3 mg/kg for 48 hrs	CSA (oral) 14 mg/kg/d Day 7 CSA (oral) 12 mg/kg/d Day 14 CSA (oral) 10 mg/kg/d	Maintain serum through levels of 50-200 ng/ml by radioimmunoassay	Pulse therapy, IV methylprednisolone (15-20 mg/kg) followed by temporary increase and then tapering of Prednisone	Lorber et al., 1987:35 Kahan et al., 1982:36 Kahn et al., 1985:288 Smith et al., 1987:155
	Prednisone 2 mg/kg (tapering to day 8)	Prednisone 2 mg/kg (tapering to day 8)	Pred 2 mg/kg Day 8 Pred 0.5 mg/kg (30 mg) 6-12 months Pred 10-15 mg/day			
University of Wisconsin						
5 Random Blood Transfusions		Pred (oral) 30 mg/d ALG 20 mg/kg/d until CSA levels are at therapeutic level	Pred (oral) 30 mg for first 21 days	Pred (oral) 10-15 mg/d		Sollinger et al., 1986:16 Stratta et al., 1987:183 1988:40
		CSA (oral) 8-16 mg/kg/d when serum creatinine at about 3.0 mg/100mL	CSA 8-16 mg/kg/d	CSA 4-8 mg/kg/d		
		AZA 25 to 30 mg	AZA increased to 1 mg/kg/d after ALG stopped	AZA 1 mg/kg/d		

Maintenance Conversion in Immunosuppression

Increasingly reports appear in the literature regarding conversion of patients from one immunosuppressive protocol to another during the maintenance period (Henricksen et al., 1986:1002; Hoitsma et al., 1987:584; Keown, 1987:1; Lennard and Venning, 1986:1149; Lennard et al., 1987:3594; Ramos, 1985:571; Shapira et al.,1986:1261; Stuart, 1985:2681; Tegzess et al., 1985:1191). Among the more interesting of these protocols are those that essentially eliminate cyclosporine. Doing so represents a major shift in the administration of immunosuppression, given the high level of enthusiasm that has been associated with cyclosporine. It, therefore, is incumbent upon us to examine the results of such studies because they have important implications for the future of transplant immunosuppression.

Based on our review of conversion studies, we find several reasons as to why this is being attempted. Gonwa et al. (1987:225) have identified the more significant reasons. These are as follows: (1) cost, (2) convenience, (3) toxicity, (4) oliogoanuria, and (5) nonresponsive rejection. Cost, of course, has become a significant concern, one addressed at length by the Task Force on Organ Transplantation (1986) in its report on "immunosuppressive therapies." Many patients have reported problems in paying for their immunosuppressive drugs, even with third-party coverage. Attempting to address this problem, legislation was recently passed to include coverage for outpatient immunosuppressive drugs for Medicare-eligible transplant recipients for a period of one-year. Historically, Medicare has not paid for outpatient medications for its beneficiaries. The provision of a one-year of coverage was based, in part, on the assumption that patients would be converted from cyclosporine therapy to conventional immunosuppressive therapy, thus, reducing their annual prescription drug costs. In general, conversion protocols, although much discussed, have not become reality. Transplant recipients continue to have very large outpatient drug expenditures, and patients still report having difficulty paying for their drugs. In some instances this has reportedly led to noncompliance and, in others, complete cessation of cyclosporine. In short, therefore, the long-term results of transplantation are at risk.

Also, it should be pointed out that third-party insurance payment on behalf of private insurers is uncertain. Since many transplant recipients fail to return to work, they often lose group health insurance coverage and, because of disability, remain Medicare beneficiaries posttransplant. Although difficult to estimate with any degree of precision, it is likely that at least one in four transplant recipients does not have insurance coverage for outpatient prescription drugs. Moreover, it is impossible to estimate the magnitude of the clinical complications that have arisen due to the absence of insurance coverage. For example, how many rejection episodes have occurred due to noncompliance? How many grafts have been lost? How many unnecessary hospitalizations have been required? All of these are important questions that bear some relationship to a patient's inability to pay for their immunosuppressive drugs.

Most recently, passage of the Medicare Catastrophic Coverage Act may be of great help to transplant recipients who are Medicare-eligible. Under provisions of this Act, beginning in 1990, Medicare will pay 80 percent of the costs of immunosuppressive drugs used after the second year after transplantation. In addition, because most transplant recipients have significant nonimmunosuppressive prescription drug expenses as well, the Act will provide further assistance. In 1991, Medicare will pay 50 percent above a $600 drug deductible; in 1992, Medicare would cover 60 percent above a limit; and in 1993 and thereafter, Medicare would cover 80 percent of the tab over a limit. The limit would be set to ensure that 16.8 percent of beneficiaries are always covered.

Other chapters in this report will further address the cost of immunosuppressive drugs and the renal transplant patient experience. What is apparent from the foregoing discussion, however, is that several critical questions require further consideration. These are as follows: (1) what is the average annual per patient expenditure for outpatient drugs under various immunosuppressive protocols? (2) What proportion of the renal transplant recipient population has both short- and long-term third-party coverage for immunosuppressive drugs? (3) What is the relationship of inability to pay for immunosuppressive drugs and patient noncompliance with therapeutic regimens? (4) What is the relationship between patient noncompliance because of inability to pay and posttransplant complications, utilization of health care services, etc? (5) What is the association between patient outcomes and noncompliance with immunosuppression due to inability to pay for outpatient drugs?

As noted above, cost is not the only consideration in decisions to convert the maintenance immunosuppression of renal transplant recipients. Transplant-related complications, such as nephrotoxicity and intractable rejection, also figure into the overall picture as well. These problems have been reviewed at length above and do not require further consideration at this time. We must ask, however, whether short-term gains attendant to conversion persist over the long-term? Also, is it conceivable that a desire to eliminate certain short-term problems with conversion gives rise to long-term complications that are even more undesirable? In short, we must consider conversion to be an issue of major significance to the future of kidney transplantation. For this reason, we have undertaken an extensive review of conversion studies to assess what the data show with respect to the efficacy of conversion.

Review

A review of a large number of clinical reports is not easily accomplished. Although it is desirable to follow a standard format when reporting results, this is not always possible because the authors of published accounts do not always include information permitting direct comparison with other reports. For example, some investigators may report graft survival rates, others may not. Sometimes such rates are described as one-year, others as six-months or two-years. Similarly, some investigators may provide very detailed information on their immunosuppressive protocols, others may provide very little information. Thus, in this review, although we have tried to report on a common set of parameters in a consistent manner, this has not always been possible. Consequently, the results of the various studies are not always directly comparable, and the conclusions arrived at in one report may vastly differ from those of another report.

In the conduct of our review, we did, however, attempt to establish each of the following:

- The location of the study.
- The number of patients studied.
- The study design (e.g., randomized, observational).

- Immunosuppressive agents used initially and at conversion.
- The time of conversion from one protocol to another.
- The therapeutic overlap (if any) for immunosuppressive drugs.
- The presence of other immunomodifying factors (e.g., blood transfusions).
- The reason patients were converted.
- Graft/patient survival rates.
- Number of grafts retained.
- Whether or not reconversion was required.
- The recommendations/conclusions of the investigators.

Obviously, the foregoing is a considerable amount of information. What is perhaps most unfortunate is the lack of uniformity in the presentation of the results from the various trials. This hampers our ability to interpret the findings of these important studies.

This review is organized by year, beginning with 1983. Although we have tried to be comprehensive, we have undoubtedly omitted a study here or a study there. Also, we should note that our definition of conversion is fairly strict. We have, for the most part, omitted studies where patients have been converted as a matter of convenience. In short, we have tried to include studies where an active research interest in conversion as long-term maintenance therapy has been the goal. Perhaps the work of Morris and his colleagues at Oxford, U.K. best exemplifies this principle. Therefore, we begin with their work.

Morris et al. (1983:273) initiated, perhaps, the earliest randomized clinical trial of a conversion protocol. In their first published account, they reported on 35 patients given an HLA-DR-incompatible cadaver kidney that was diuresing immediately after transplantation. These patients were randomly allocated to treatment with cyclosporine alone for three months, followed by conversion to conventional treatment--azathioprine and prednisone. Although many patients had to be converted to AZA + PRED before 90 days because of rejection requiring more than two treatment courses of high-dose, intravenous methylprednisolone, 16 of 21 grafts were functioning at three months, and 12 of 14 grafts in the control group were functioning. However, three further grafts were lost from chronic rejection in the control group, and nine were lost from chronic rejection in the CSA group. All but one patient on CSA had depressed renal function, and in all of these patients function improved with conversion to AZA + PRED. This depression of renal function was attributed to both the cyclosporine nephrotoxicity and to a low-grade rejection reaction, the latter suggesting that the addition of steroids to cyclosporine might be beneficial to some patients. Morris et al. concluded that "... the strategy of a three-month course of cyclosporine followed by conversion to AZA + PRED provides satisfactory immunosuppression, and may be of value if long-term side-effects of cyclosporine emerge with further experience."

In the study by Morris et al., it is important to note that patients were randomized, that 57 percent of the CSA patients were not transfused compared with 14 percent of the AZA + PRED patients, and 24-month graft survival rates for both groups were approximately 58 percent. The primary reason for conversion were lymphomas and nephrotoxicity.

In another study, Rolles et al. (1983:2878) reported on 101 patients, 16 of whom were converted at two weeks to 34 months (mean = 5.6 months). This was an observational study that took place at Addenbrooks Hospital

(Cambridge, UK) between July, 1978 and December, 1982. Patients initially received CSA monotherapy and were converted to AZA + PRED. A therapeutic overlap of three to five days was allowed. There were no other immunomodifying factors identified. Uncontrollable rejection was the primary reason for conversion. For the CSA monotherapy group, graft survival was 73 percent, and patient survival 88 percent. For the AZA + PRED group, graft survival was 50 percent, and patient survival 78 percent. Finally, for the converted group, the three-year graft survival rate was 50 percent and patient survival 78 percent. Fourteen AZA + PRED patients were eventually converted to CSA. The authors concluded that conversion was successful in one-half of the patients whose kidneys were rejecting.

Land et al. (1983:2857) in Munich studied 195 patients, 30 of whom were converted. The converted patients were divided into three groups. Group one consisted of 18 patients with good renal function who were randomized (age = 19-61 years). Group 2 consisted of 14 patients with uncontrollable rejection (age = 25-51 years). Group 3 consisted of patients with nephrotoxicity or a nonfunctioning or poor graft (age = not stated). Patients in Groups 2 and 3 were not randomized. All patients initially received CSA + PRED + METHYLPREDNISOLONE. At conversion, patients received ALG or ATG and were put on AZA + PRED maintenance therapy. Conversion for each group occurred as follows: Group 1, at three months; Group 2 at 1-6 months; Group 3, at least 2-12 months after transplant. There was overlap in immunosuppressive protocols, but the time period was not specified. No other immunomodifying factors were noted. Graft retention varied by group. In Group 1, there were three graft losses in the converted group and one loss in the control group. In Group 2 there were four graft losses, but three patients had their rejection reversed. In Group 3 there were three graft losses. In Group 1, three patients were reconverted to CSA.

Based on their findings, Land et al. concluded that their study was discouraging and that the results did not compare well with those of the Oxford group. In desperate cases they indicated that conversion was worth a try, but there was a need to investigate other conversion protocols at different points in time.

Wood et al. (1983:2862) later provided additional information on the Oxford trial. They describe two trials--Trial I and Trial II. Trial I began in January, 1980 and ended in November, 1981. It included 35 patients, 21 of whom were randomized to CSA and 14 to AZA. Trial II began at the close of Trial I and included 66 patients. Between the two trials, 34 patients were randomized to CSA and 32 to AZA. Patients initially received CSA monotherapy and were randomized to AZA + PRED with a short course of methylprednisolone. At 90 days, 55 patients had been converted in both trials, although six patients were converted before 90 days. There was no therapeutic overlap.

In Trial I, only HLA-DR mismatched patients were included. Patients with hepatic dysfunction or malignancy were out, as were recipients of living related donor grafts. Trial II consisted exclusively of recipients of cadaver grafts, again patients with liver disease or malignancy were excluded. Some patients in both trials received blood transfusions. The reasons for conversion were as follows: lymphomas, nephrotoxicity, interstitial fibrosis, hypertrichosis, gum hypertrophy, tremor, hyperaesthesia, and gastrointestinal problems. Minimum followup in Trial I was 18 months and in Trial II, nine months.

Graft and patient survival rates for the Oxford trials are shown in Table 3-24. Fifty percent of the CSA patients in Trial II required dialysis initially, compared with 34 percent of the AZA + PRED patients. In the converted patients there was a fall in the serum creatinine. Of 30 converted patients, 6 had acute rejection within the first two weeks. The investigators concluded that conversion at three-months was feasible. They also noted that improved renal function was due to the abolition of CSA nephrotoxicity rather than control for low grade rejection. Twenty percent of the patients, unfortunately, had acute rejection following conversion. In response to this, Wood et al. suggested that, perhaps, therapeutic overlap is indicated.

In an observational study of ten patients experiencing nephrotoxicity, Flechner et al. (1983:2869) indicated positive results following conversion. The patients were 8 to 55 years of age, seven had cadaveric grafts and three living related donor grafts. Six of these patients had previously had rejection therapy. The patients were started on a CSA + PRED protocol and were converted to AZA + PRED. There was five to seven days of therapeutic overlap between regimens. Two grafts were lost after conversion. The investigators reported that no patient experienced significant rejection at conversion, and 9 out of 10 patients had improved renal function. At 208 ± 79 days followup, eight patients had functioning grafts, however, concern was expressed with "breakthrough" rejections.

For the period April, 1980 through April, 1983, Canafax et al. (1983:2874) have reported on their results with 159 patients, 28 of whom were converted in an observational manner. Seventy-one percent of these patients were male and 50 percent diabetic. Patients initially received CSA + PRED or AZA + PRED + ALG. In the "early" group, conversion occurred at 40 ± 16 days, the

Table 3-24
Graft and Patient Survival Rates in the Oxford Trials

	Trial I		Trial II	
Survival	CSA	AZA+PRED	CSA	AZA+PRED
GRAFT	71%	57%	79%	70%
PATIENT (COMBINED)	91%	90%		

SOURCE: Wood *et al.*, 1983:2862

"late" group at 215 ± 84 days, and overall at 154 ± 111 days. In seven patients, ALG was used at time of conversion. Eighty-two percent of the patients had received cadaveric grafts and nine regrafts. The reasons for conversion were as follows: persistently elevated serum creatinine levels, in the absence of obstruction, renal arterial stenosis, or rejection. In this study, five patients died, two while on hemodialysis. Eighty-six percent of the ALG patients developed serious infections. Three of these patients died from infections. Two of seven deaths were unrelated to conversion. Thirty-six percent of the patients developed leukopenia, and 14 percent of the patients had rejection episodes after conversion. Risk factors for conversion are believed to be the following: (1) cadaver grafts, (2) ALG, (3) diabetes, and (4) regrafts. The investigators note that the fear of acute rejection after conversion is unwarranted.

Only one study was published in 1984 that we reviewed, this by Rocher et al. (1984:669) at Brigham and Women's Hospital. During the period March, 1983 through March, 1984, fifty-seven patients were converted (43 cadaver, 14 non-HLA identical living related donor, three diabetic nephropathy, 38 male, 19 female, age = 39 ± 12 years). Patients were divided into three groups.

- Group 1 = 10 patients with prolonged graft nonfunction.
- Group 2 = 8 patients with active rejection unresponsive to treatment.
- Group 3 = 39 patients with stable functioning grafts.

For all patients the initial immunosuppressive protocol was CSA + PRED. The conversion protocol was AZA + PRED. All patients were electively converted at four months. Therapeutic overlap was three to five days. Primary reasons for conversion, in addition to what was noted above, included:

nephrotoxicity, interstitial fibrosis, hepatotoxicity, and life threatening infection.

The results of the study by Rocher et al. varied by group over a followup period of 5 ± 3 months. In Group 1, 6 of 10 patients regained function and their creatinine declined. Four grafts were lost. In Group 2, five of eight patients had controlled rejection. All eight patients were alive but two grafts were lost. In Group 3, 27 patients had improved graft function, seven stable function, and two had their renal function decline further. One graft was lost. Out of 57 patients, only one lost graft function because of acute rejection, although acute rejection was the most common problem. The rate of infectious complications was considered high. The investigators recommended that patients with prolonged early nonfunction be converted.

The majority of conversion studies were published in 1985. Adu et al. (1985:392) reported on 12 adult, nondiabetic patients, five of whom were converted in a prospective randomized study. Patients were initially placed on CSA + PRED with conversion to AZA + PRED at 11 weeks. Reduced renal function was the primary reason for conversion. One patient died, and three had acute rejection episodes. Four out of five grafts were retained, but two patients were reconverted. The investigators concluded that "conversion is disastrous."

Chapman et al. (1985:128) provide additional information on the Oxford prospective randomized trial involving 86 patients. Sixty-two were selected for study whose grafts had functioned at 120 days. They initially received CSA monotherapy and were converted to AZA + PRED at 90 days. The reason for conversion was reduced renal function. The investigators conclude that nephrotoxicity is reversible by conversion to AZA + PRED and that long-term graft survival is likely to improve.

Aslaman and his colleagues (1985:1066) at Cardiff conducted a prospective randomized study of 52 patients. Twenty-six patients were placed on CSA monotherapy with prednisone added upon rejection. Another 26 patients were placed on CSA + AZA + PRED with the CSA discontinued gradually after three months. The purpose of this study was to achieve better results with fewer complications. There were six patient deaths in the converted group, and 19 of 26 converted patients had functioning grafts at followup. The investigators concluded that triple therapy may be "safe" for uncomplicated patients, but that triple-drug patients had more infections and were at high risk of death.

In a subsequent report, Flechner et al. (1985:1227) updated the results from Houston for the period January, 1981 through June, 1984. A total of 281 patients were studied, 250 of whom received CSA + PRED and 31 of whom were converted (18 males, 13 females, age 20-55 years, 22 cadaveric, 9 living related donors). Patients were converted due to nephrotoxicity and for financial reasons. The converted patients were divided into three groups:

- Group 1 = 13 patients converted without a history of rejection. Conversion occurred at 254 ± 195 days.
- Group 2 = 13 patients with a history of rejection while on CSA. Conversion occurred at 232 ± 190 days.
- Group 3 = 5 patients who did not respond to rejection therapy. Conversion occurred within two weeks posttransplant.

The results of this study varied by group. In Group 1, Group 2, and Group 3, three, seven, and five grafts were lost, respectively. The investigators urged caution in the selection of patients for conversion. In particular, they found that patients with rejection before conversion did not benefit, prompting them to argue against a policy of routine conversion of all CSA patients during the maintenance period. Finally, Flechner et al. insisted that conversion is not useful for patients with steroid-resistent rejection.

Wood and coworkers (1985:1164) at Oxford provided a further update on the results of their ongoing research--a trial which began in November, 1981. At this point, 115 cadaveric kidney transplant recipients were available for analysis. Some patients were regrafts. All patients initially received CSA monotherapy. At day 90, 60 patients were randomly assigned to AZA + PRED. The patient groups were similar with respect to age, sex, HLA-A,-B, and -DR matching, preoperative blood transfusion status, and number of first grafts and retransplants. Patients were considered for conversion because of lymphomas, nephrotoxicity, and hepatotoxicity. One-year graft survival for the CSA group was 71 percent, and 61 for the AZA + PRED group. The CSA regrafts did better than the AZA + PRED regrafts (CSA = 81%, AZA + PRED = 25%). Blood transfusions also positively influenced the results with CSA (82% with transfusions, 50% without transfusions). Patient survival in both groups was 90 percent. One graft was lost following conversion, and rejection following conversion appeared to be a problem (19%). Four patients required reconversion to CSA. The mean followup for all patients was 17.6 months (1-33 months). CSA patients had a high mean serum creatinine which fell following conversion. The investigators concluded that conversion is feasible with better graft survival rates achievable than under conventional immunosuppressive protocols that exclude CSA.

Vanrenterghen et al. (1985:1162) reported on a randomized trial of 18 first cadaveric graft patients transplanted between February, 1983 and

September, 1983. All patients initially received CSA + PRED. At 30 days, 9 patients were converted to AZA + PRED (Group 1) and at 90 days, 9 patients were converted to AZA + PRED. Two days of therapeutic overlap was permitted. Patients were converted because of long-term side-effects. During the first month posttransplant, when all patients were on CSA, there was one patient with rejection in Group 1 and five patients with six rejections in Group 2. Three patients in Group 1 required reconversion, while one patient did so in Group 2. The investigators noted that conversion from CSA to AZA + PRED was rapidly followed by an acute, although reversible, rejection episode in more than 80 percent of the patients. The investigators were disappointed with their results, stopped the study, and went back to continuous administration of CSA. They found, however, that there were many more rejections after conversion.

Of 135 transplants, McDonald et al. (1985:1940) reported on 15 patients (cadaver + living related) who were converted during the period December, 1980 through December, 1983. The study was observational. All patients started with a CSA + PRED protocol, but the PRED was only administered every other day. The conversion protocol consisted of AZA + PRED. Patients were converted because they were not doing well on CSA, with nephrotoxicity and rejection as primary problems. The authors reported that the nephrotoxic patients improved and that one of six rejecting patients improved. They noted that if graft function was unstable, switching could be a problem. Five of six patients became worse after conversion. Of the nine patients with uncertain diagnosis, early improvement was followed by rejection in five patients.

Canafax et al. (1985:1176) summarized their results in an observational study of 243 patients in Minneapolis. Thirty-six patients were converted to AZA + PRED, seven patients were converted with ALG, sixty patients received CSA + AZA + PRED, and 140 patients remained on CSA + PRED. The seven patients converted with ALG received ALG for 10 days. Therapeutic overlap lasted for three to seven days. Patients were converted for many reasons--nephrotoxicity, prolonged ATN, acute rejection, neurotoxicity, and hyperkalemia. Five patients died with functioning grafts in the ALG group. The investigators reported that renal function improved in response to complete conversion with the addition of AZA. Graft survival improved for CSA + AZA + PRED patients. The authors argued that ALG should not be used during conversion. They also found that conversion led to acute rejection and that complete conversion to AZA + PRED led to leukopenia. Finally, the gradual addition of AZA to CSA + PRED was particularly helpful.

The Brigham group has provided additional followup on their series (Carpenter et al., 1985:261) of 48 or 49 patients who were converted. Twelve patients were converted for primary nonfunction and a second group was converted for poorly controlled rejection. Initially patients received CSA + PRED according to two dose schedules. Patients were converted to AZA + PRED at four months or more. During conversion there was five days overlap as CSA was tapered. It should be noted that the cadaveric patients received random blood transfusions (> five units). Living related donors did not receive transfusions. Followup extended over a period of 7 to 36 months. The incidence of acute rejection after conversion was 30 percent. Unsatisfactory results were achieved in 6 of 48 patients converted. There was a significant incidence of acute and chronic rejection. Clearcut benefits were conferred on a small number of patients. Carpenter et al. cautioned that reconversion may be necessary.

In another report, Flechner et al. (1985:276) reviewed their experience with 39 patients converted during the period January, 1981 through January, 1985 (22 males, 16 females, 19-55 years of age, 31 primary grafts, 28 cadaveric, 10 living related donors, one child was excluded from this analysis, therefore N = 38). Patients were divided into three groups, as follows:

- Group 1 = 16 patients converted without previous rejection.
- Group 2 = 13 patients converted for persistent renal dysfunction.
- Group 3 = 9 patients who responded poorly to antirejection therapy.

All patients initially received CSA + PRED and were converted to AZA + PRED. The time of conversion varied by group as follows: Group 1 = 248 ± 217 days, Group 2 = 249 ± 186 days, and Group 3 = 185 ± 199 days. There was therapeutic overlap as CSA was tapered over several days. In Group 1, four grafts were lost. In Group 2, nine grafts were lost. In Group 3, all grafts were lost. Flechner et al., at one to two years followup, reported that there were no immediate problems associated with conversion and that no rejections occurred during switching. All Group 3 grafts were lost within two months. The risk of rejection after conversion appeared to be substantial. Based on this experience, Flechner et al. abandoned complete conversion and, instead, lowered the dose of CSA and added AZA to their protocol for problem patients.

Chapman and Morris (1985:254) have followed up 129 patients with cadaveric grafts. Transplants were performed between November, 1981 and November, 1984. The study was randomized prospective with all patients initially placed on CSA monotherapy. Conversion to AZA + PRED was accomplished by 90 days, although 11 patients were converted before 90 days. Patients were converted in an effort to avoid the long-term disadvantage of cyclosporine nephrotoxicity, as well as concerns about cost, disgusting taste, and hirsutism. Patient and graft survival rates are reported in Table 3-25, although no figures are provided for the converted patients, specifically. Twenty-eight percent of the patients had acute rejection in the first month after conversion, and two patients were reconverted. The investigators reported that AZA patients were less likely to pass urine in the early period. Creatinine levels clearly fell following conversion, as did blood pressure. Unfortunately, conversion could result in graft loss and conversion was of no help when the graft was rejecting or not functioning. Still, however, Chapman and Morris suggested that their conversion protocol "confers detectable advantages."

A report by Thistlethwaite and coworkers at the University of Chicago is particularly interesting because it attempted to estimate the financial impact of conversion (Thistlethwaite et al., 1985:314). Of a total of 86 patients, 27 were converted. Only stable patients were converted at six months. Patients had no documented episodes of rejection prior to conversion. The initial protocol consisted of CSA + PRED and the conversion protocol was AZA + PRED. A four-day therapeutic overlap was allowed. Key characteristics of the patients are presented in Table 3-26. Patients were primarily converted for financial reasons, although nephrotoxicity, hepatotoxicity, and lymphomas were all concerns. No allografts were lost after conversion. The authors report that the annual cost of cyclosporine for

Table 3-25
Patient and Graft Survival Rates in the Oxford Series

Patient Survival	1 Year	2 Year
CSA	92%	92%
AZA+PRED	95%	95%
Graft Survival		
CSA	73%	73%
AZA+PRED	58%	51%
Regraft Survival		
CSA	75%	75%
AZA+PRED	25%	25%

SOURCE: Chapman and Morris, 1985:254.

Table 3-26
Characteristics of Patients in the University of Chicago Conversion Study

Female/Male Ratio = 17/10

LRD/CAD Ratio = 5/22

AGE $\bar{X}$ = 37 (14-60 years)

CAD HLA-A,-B match $\bar{X}$ = 1.33

CAD HLA-A,-DR match $\bar{X}$ = 0.44

% transfused initially = 22%

% first graft = 71%

% highly sensitized (40% panel) = 19%

% rejection before conversion = 26%

SOURCE: Thisthlethwaite *et al.*, 1985:314

a 70 kg person was over $4,000, while the cost of AZA was less than one-tenth that amount. At three-months, patient drug costs equalled $1,520 and at six-months, $2,451. Forty-one percent of the patients in the study had third-party coverage for drugs. Followup for these patients was 4 to 10 months. Of the 27 patients, 15 percent had acute rejection. Of the patients not having rejection, renal function improved. While previous studies have looked at unstable patients, this study looked at stable patients but, even still, breakthrough rejection could be a problem in more conservative studies. In this study, no patient with a history of prior rejection had a rejection after conversion, although chronic rejection may occur.

Morris et al. (1987:586) have provided additional followup on 129 cadaver renal transplants performed at Oxford between November, 1981 and November, 1984. Sixty-four patients initially received CSA monotherapy and were converted to AZA + PRED at 90 days posttransplant, although 26 patients were converted before 90 days. Additionally, 65 patients were randomized to AZA + PRED and never received CSA. Other immunomodifying factors were present--some patients received transfusions, HLA-DR compatibility was present, and the conversion group had more HLA-A and -B, mismatches. Patients were converted because of concerns with nephrotoxicity and lymphomas. Patient survival in the conventional group at one and four years was 94 percent compared with 92 percent in the conversion group. Graft survival rates at one and four years for the AZA + PRED group was 59 percent and 47 percent, respectively. In the converted group, the comparable rates were 72 percent and 67 percent. Thus, the graft survival rates by protocol differed significantly. Three grafts were lost late among conversion patients, while seven grafts were lost in the AZA + PRED group. Followup was complete at between 24 and 60 months. Good renal function was restored in the converted patients, although 32 percent of the patients had acute rejection episodes following conversion. Late rejection with conversion remained an issue, as did late nephrotoxicity and cardiovascular problems.

The Leiden experience has been reported by Paul et al. (1987:917) for 68 patients randomized prospectively. Thirty-two patients received AZA + PRED only, 18 were placed on CSA monotherapy, and 18 patients began with CSA monotherapy but were converted at three-months to AZA + PRED. Patients were converted because of concerns related to nephrotoxicity and a desire to achieve better graft survival rates. Two of 18 patients converted required rejection therapy, and one of 18 of the patients on CSA monotherapy required rejection therapy. Eleven of 32 patients on AZA + PRED only required rejection therapy after three-months. At three months, the CSA-only patients had poorer graft function. At six months there were no differences in graft function among any patients. The AZA + PRED patients were found to have the best graft function at twelve months. The investigators concluded that the risk of graft loss after conversion was not significant.

Versluis et al. (1987:387) have summarized the Rotterdam experience with 41 nondiabetic cadaver kidney transplants. Twenty-three patients initially received CSA and were converted at one-year to AZA + PRED. Seven patients in this group had regrafts. In this observational study, the remaining patients received CSA monotherapy. There was no rejection crisis in the six-months prior to conversion. The primary reason for conversion was nephrotoxicity. Graft survival for the conversion patients was 81 percent, and for the CSA patients, 95.3 percent. Followup was for six months to 18 months. Four of seven regrafted patients rejected upon conversion.

All patients who were switched experienced a fall in their serum creatinine, their creatinine clearance improved, and their blood pressure fell. The investigators concluded that one-year of CSA monotherapy did not cause permanent structural damage in the kidneys.

The Iowa City experience has been considered by Gonwa et al. (1987:225). One-hundred-ten cadaveric transplants were performed between December, 1983 and August, 1985. Seventy-eight of these were primary grafts and 38 were retransplants. All patients were started on CSA and PRED. Of the 110 patients, 46 were converted from CSA to AZA for a variety of reasons (cost, toxicity, patient preference, prolonged dysfunction posttransplant, or nonresponsive rejection). In this observational study, all patients were divided into five groups, as follows:

- Group 1 = N=16, stable primary transplant converted for cost, nonrenal toxicity, patient preference; serum creatinine less than 2 mg/dl.
- Group 2 = N=6, primary transplants converted for presumed toxicity; serum creatinine greater than 2.5 mg/dl.
- Group 3 = N=7, retransplants converted for cost, nonrenal toxicity, or patient preference; serum creatinine less than 2 mg/dl.
- Group 4 = N=8, prolonged poor function posttransplant; serum creatinine greater than 4 mg/dl or patient on dialysis.
- Group 5 = N=9, nonresponsive rejection; serum creatinine greater than 4 mg/dl or patient on dialysis.

Conversion occurred at between 1.4 and 16.0 months posttransplant. Sixteen grafts were lost across all groups and there were three patient deaths. Followup varied between 11.5 and 16 months. The investigators concluded that only stable primary grafts should be converted to avoid toxicity problems. They reported that the renal function of CSA patients did not differ from that of AZA patients. CSA to AZA conversion may lead to chronic rejection. The main benefit of CSA may be in the first six-months posttransplant, although Gonwa et al. found it difficult to predict which patients could be safely converted.

Further review of the Oxford randomized study has been provided by Chapman et al. (1987:860). In this report 110 patients were considered, of which two were regrafts. Fifty-two of these patients were placed on CSA monotherapy and 58 on AZA + PRED. At 90 days the CSA patients were randomized to AZA + PRED. Two reasons for conversion were reported--nephrotoxicity and blood pressure. No data were provided on graft and patient survival rates. Numerous findings are of interest, however. CSA patients had a higher serum creatinine at conversion than did AZA patients. After conversion the creatinine levels fell to the level of the AZA patients. Serum potassium levels also fell after conversion, and the percent of patients with hypertension was reduced. During the first three months AZA patients generally had blood pressure higher than CSA patients. Also, the authors noted that patients on AZA + PRED and the conversion patients had higher blood pressures than the CSA only patients. This, in their minds, raised questions as to the possible adverse consequence of continuous steroid exposure.

The Houston experience is further highlighted by Lorber et al. (1987:476). Lorber and his colleagues reported on all (N=360) patients transplanted between January, 1981 and June, 1985. Of these patients, 59 required a protocol change. Thirty-four were switched because of toxicity and 25 because of rejection. All patients were initially treated with CSA + PRED. Twenty-five patients were converted to AZA + PRED at 246 ± 185 days. Twenty-four patients were converted to CSA + AZA + PRED at 387 ±

323 days. This series included both living related donor and cadaveric donor recipients. Survival rates for the various patient groups are summarized in Table 3-27. The comments/recommendations of the Houston group are of interest. Patients who were converted to AZA + PRED because of nephrotoxicity had differing outcomes depending upon their experience with previous rejection. Patients with previous rejection were more likely to have rejection (85 % vs. 58 %), more likely to have graft loss (77 % vs. 50 %) and more likely to have infection (46 % vs. 0 %). There was no leukopenia in the triple drug group. Followup for the CSA + AZA + PRED group was 420 ± 180 days. All triple drug patients were dialysis independent after initiation of triple drug therapy, although renal function was not completely normal. Four triple drug patients had liver dysfunction, and 15 percent of these patients did not tolerate CSA + PRED. Patients on AZA + PRED had a higher rate of rejection, while the complications associated with CSA + PRED + AZA were largely infectious.

Hoitsma et al. (1987:584) from the Netherlands have updated the results of their conversion study. A total of 143 patients were included in a prospective randomized study. Seventy-two of these patients received CSA + PRED and were converted to AZA + PRED at 90 days (7 patients were converted before 90 days). Seventy-one patients received AZA + PRED. Nephrotoxicity and a desire to improve results were the primary reasons for conversion. With 15 months followup, one-year graft survival rates were as follows: CSA + PRED = 80 percent, AZA + PRED = 70 percent. Patient survival rates were 94 percent for the converted patients and 97 percent for the AZA + PRED patients. After conversion, eight grafts were lost in the CSA group, and 12 grafts were lost in the conventional group.

Table 3-27
Survival Rates at the University of Texas--Houston

Maintenance Protocol	1 Year	2 Year	4 Year
GRAFT SURVIVAL			
CSA + PRED	78%	N/P	71%
AZA + PRED	40%	29%	N/P
CSA + AZA + PRED	100%	84%	N/P
OVERALL PATIENT SURVIVAL	95%		90%

N/P = not provided

SOURCE: Lorber *et al*., 1987:476

Hoitsma et al. report that rejection episodes were higher in the AZA group, but after dropping CSA, toxicity was eliminated and hypertension was reduced. They concluded that the advantages of CSA are not lost after conversion and that conversion, therefore, is safe.

The results of a major multicenter comparison of three immunosuppressive regimens in cadaver renal transplantation was recently published by the Australians (Hall et al., 1988:1499). This randomized trial was conducted in seven hospitals to assess the safety and efficacy of the various protocols on primary graft patients. The three protocols were as follows: (1) long-term CSA, (2) short-term (3-months) CSA followed by AZA + PRED, and (3) AZA + PRED without CSA. Patients assigned to long-term CSA (N=138) or short-term CSA followed by AZA + PRED (N=141) had a similar actuarial 12-month survival (98.4 % vs. 96.4 %) and graft survival (83.9% vs. 82.1%). Patients assigned to receive only AZA and PRED (N=138), with optimal use of antithymocyte globulin, had a significantly poorer survival rate (91.3%, $p = 0.015$), because of deaths from cardiac causes and infection, but their graft survival of 76.0 percent ($p = 0.31$) did not differ significantly from that of either group receiving CSA.

After switching from CSA to AZA + PRED, 15 percent of patients had reversible rejection episodes, but the frequency of rejection and graft loss did not differ from that in the long-term CSA group. After the change to AZA + PRED, serum creatinine levels declined in nearly all patients, so that after three months they were comparable to those in the group receiving AZA + PRED only, and significantly lower than those in the group receiving long-term CSA therapy ($p < 0.003$).

Hall et al. (1988:1499) concluded that "... the cyclosporine regimens result in comparable patient and graft survival, but that changing to azathioprine and prednisolone at three-months improves graft function."

To conclude this review, we will summarize the results of eight conversion studies presented at the Second International Congress on Cyclosporine. These studies are instructive and most were presented by investigators who have not previously published their results or, if they have, the studies, in some instances, included approaches to immunosuppression that differed from early reports. For example, the Minnesota report reviewed below includes an analysis of quadruple therapy.

Ford and colleagues (1988:8) reported on 246 recipients of renal allografts from cadavers (158) and from mismatched related donors (88) that were first stratified by risk, and then prospectively randomly assigned either to the group receiving CSA + PRED (131), or to the group receiving AZA + PRED (115), after two weeks of MALG to induce immunosuppression. Prior to transplantation, all patients had received multiple blood transfusions from at least five different donors, and had undergone splenectomies. The number of diabetic elderly, and secondary graft patients was evenly distributed between the two groups.

Graft and patient survival rates between the two groups did not differ, although the incidence of posttransplant acute tubular necrosis (ATN) in the immediate posttransplant period was higher in the CSA + PRED group than the AZA + PRED group. In addition, the AZA + PRED patients with ATN regained their kidney function more quickly than the CSA + PRED patients, and their serum creatinine at discharge was also lower. Nearly 83 percent of the CSA + PRED patients showed evidence of nephrotoxicity.

Based on these data, the Minnesota group decided to gradually reduce the doses of CSA to deal with nephrotoxicity. Other indications for changes in therapeutic protocol included delayed graft function, hypertension, neurotoxicity, and, in some cases, acute rejection and cost.

In some patients AZA was substituted for CSA, and, in others, AZA was added to the protocol. Serum creatinine levels improved in nearly all patients. Moreover, most patients who had been on dialysis prior to the addition of AZA recovered their renal function and no longer required dialysis. Patients with delayed graft function or acute rejection as the main reason for changing the immunosuppressive regimen accounted for the majority of graft losses in the converted patients. In patients who were switched to AZA + PRED, the addition of MALG in order to prevent graft rejection at the time of conversion resulted in serious, and often fatal complications in four of the seven patients in whom this was tried.

Based on the results of their various studies, the Minnesota group went on to conduct an additional noncomparative study using two immunosuppressive protocols: AZA + CSA + PRED for recipients of mismatched related, and AZA + CSA + PRED + ALG for recipients of cadaver renal allografts. This study suggests that triple or quadruple drug therapy with AZA + CSA + PRED ± ALG is a very effective immunosuppressive regimen for transplanting HLA-mismatched, cadaveric, and female recipients. In addition, heavily sensitized recipients and recipients of multiple renal transplants may also benefit from triple drug therapy. This approach allows induction of immunosuppression with ALG and AZA, delay in adding CSA, and relatively low maintenance doses of PRED. Graft survival rates were slightly better in the triple therapy group then in the CSA + PRED group. Although patient survival rates were the same, there was a significant reduction in the incidence of nephrotoxicity, duration of ATN, and hospital stay in the patients receiving AZA + CSA + PRED ± MALG.

In summary, the Minnesota group has found that the combination of AZA + CSA + PRED + MALG, with CSA delayed until serum creatinine is normal (in cadaveric transplants) is very efficacious. The benefits of all four agents are realized, and by limiting MALG to a maximum of seven days, viral infections are avoided, as are the toxic effects of the other agents. Since July 1, 1984 the foregoing has been the standard immunosuppressive regimen at Minnesota.

Oka and colleagues (1988:143) have provided a report on their experience with living related kidney transplant recipients who were converted totally from cyclosporine to azathioprine. Eighty-one patients were studied during the period April 1982 through August 1986. Patients initially received CSA + PRED. Acute rejection crises were treated with bolus doses of methylprednisolone. Twenty-two patients remained on CSA while 59 patients were converted from CSA to AZA. Thirty-nine patients were totally converted while the remaining twenty patients received CSA + AZA. The outcomes of the two conversion groups were evaluated.

Acute rejection, although reversible, occurred in 13 of 39 patients (33.3%) after total conversion, and in only one of 20 patients (5.0%) after overlap therapy of CSA + AZA. These differences were significant. Temporary hepatic dysfunction and leukopenia were observed in 39 patients after total conversion, but not in any of the 20 patients receiving overlap therapy. After total conversion to AZA, graft survival rates were 77 percent at one year, 72 percent at two years, and 70 percent at three and four years.

For patients on CSA + PRED, cumulative graft survivals were 95 percent at one to four years after conversion.

In the foregoing study, total conversion to AZA or conversion to a combined therapy of CSA + AZA was designed to minimize the effect of persistent nephrotoxicity on long-term graft outcome in living-related kidney transplantation. Unfortunately, many more problems, including graft loss, were encountered with total conversion to AZA.

Maddux and associates (1988:152) have reported on 110 renal allograft recipients transplanted between January 1, 1984 through December 31, 1985. All patients initially received CSA + PRED but were converted from CSA because of the following: (1) persistent CSA side-effects, unresponsive to dosage reduction, (2) posttransplant acute tubular necrosis (ATN) of more than two weeks duration, (3) stable renal function noted at least six months following transplantation and a desire to reduce expense of outpatient medications, and (4) noncompliance with the prescribed CSA regimen. A control group of 21 matched patients selected from the nonconverted population was observed concurrently.

Twenty-one converted patients were switched to AZA, an average of 5.1 ± 3.0 months posttransplant. The investigation indicated that stable patients may be safely converted from CSA to AZA without penalty of infection, rejection, or allograft loss. Postconversion complications (infection, rejection, leukopenia) were minimized. ALG therapy was avoided, something which the investigators feel minimized complications postconversion. History of prior acute rejection did not appear to be a contraindication to conversion. Conversion had a beneficial effect on renal function when compared with the preconversion period. Also, conversion resulted in an annual savings per patient of over $2,000. The authors, therefore, conclude that CSA is cost-beneficial.

The results of a study by Sagalowsky et al. (1988:157) indicate that late cyclosporine conversion carries the risk of irreversible rejection, although only a small number of patients were studied. All patients initially received quadruple induction with intervenous ALG and oral prednisone. Ten patients randomized to Group 1 began oral AZA at entry into the protocol and the CSA dose was gradually decreased to zero over six weeks. Nine patients randomized to Group 2 remained on CSA with gradual dose reduction.

Sixty percent of the Group 1 patients had an episode of acute rejection. Five of these patients responded to steroids, the sixth patient lost his graft. Two patients developed leukopenia requiring discontinuation of AZA. Two patients developed new liver enzyme elevations. Only three patients remained successfully converted, while seven patients were restarted on CSA.

Among the Group 2 patients, there were no episodes of acute rejection, and none of the nine patients required discontinuation of CSA. Mean serum creatinine levels were lower after the CSA dose was decreased than at entry into the study.

The investigators concluded that elective gradual cessation of CSA over six weeks with full coverage of AZA in stable cadaver renal transplant recipients one year following transplantation is associated with a high risk of acute rejection that may prove unresponsive to therapy and result in graft loss. There was no evidence of chronic CSA-related nephrotoxicity in patients remaining on low dose CSA.

Jacobsen et al. (1988:155) have reviewed their experience with conversion immunosuppression in 1983 cadaver and 42 living-related donor renal allografts. Patients initially received a triple regimen of CSA + PRED. Some patients, in the early experience, received methylprednisolone with the induction of anesthesia. Conversion to AZA took place after three months. For one week a triple regimen was followed, after which CSA administration was stopped.

In the living related group one patient developed deep vein thrombosis that was complicated by septicemia. The patient later died. None of the other grafts were lost, but there was a disturbingly high incidence of rejection episodes (22 %) that were managed with bolus doses of 500mg each of MP for three consecutive days. In the cadaver group, however, despite early optimism, there was a 56 percent incidence of rejection episodes, five deaths occurred and 13 kidneys were nephrectomized within three months of conversion. Patient survival after 12 and 45 months was 94 percent and 93 percent and graft survival was of 79 percent and 64 percent.

Hoitsma and associates (1988:161) have provided further followup on the trial described in previous publications reviewed above. Between July 1983 and June 1987, 181 patients received cadaveric grafts. The mean follow-up of the patients was 17.1 ± 14.2 months (range, 3 to 48 months). The male-female ratio was 1:4, and the mean patient age was 42 ± 13.3 years (range, 15 to 68 years). Patients initially received CSA + PRED. At ninety days posttransplant, CSA was stopped and AZA was started. The PRED dose was increased temporarily and then decreased daily to a maintenance dose of 10mg daily.

During the first three months, 34 percent of the patients experienced at least one rejection which was significantly lower than the 77 percent observed among patients receiving conventional immunosuppression. Graft loss occurred in 14 patients during this period, but in only three patients was this due to rejection. Conversion before the end of three months was necessary in 25 patients, mainly because of nephrotoxicity. Seven patients were not converted because of persistent leukopenia or thrombopenia. In 135 patients, conversion was carried out according to the treatment protocol. Serum creatinine and mean arterial pressure levels decreased significantly after conversion. Three-month graft and patient survival rates were 92 percent and 98 percent, respectively, and at one year, 80 percent and 92 percent, respectively. Eighteen patients lost their grafts after conversion, and in eight patients graft loss was due to chronic rejection.

The authors concluded that conversion after transplantation from CSA to azathioprine at three months can be done safely without occurrence of intractable rejections. Moreover the authors note that "... most of the immunologic failures due to chronic rejection seem to be a result of earlier immunologic damage already occurring during the first three months of CSA treatment."

Abbud-Filho and colleagues (1988:164) from Sao Paulo, Brazil report on 46 patients who received a renal transplant that were initially treated with CSA + PRED. Twenty-three patients were later switched to AZA+PRED, the remaining 23 patients continued on CSA therapy. Conversion to AZA + PRED was accomplished by adding AZA and reducing CSA doses by 50 percent every two weeks, thereby producing a 15-day overlap period.

Only one patient had a reversible episode of acute rejection 15 days after conversion. Throughout the follow-up period, five of 23 (22%) patients in the CSA group had experienced nine episodes of acute rejection, while in the AZA + PRED group 16 episodes of acute rejection were observed in 12 patients (52%). Analysis of renal function between the groups for each corresponding period of time did not show any statistical difference, although creatinine clearance values were slightly better for AZA + PRED than for CSA-treated patients. A higher incidence of hypertension was observed among the CSA-treated patients. Patient and graft survival rates for the two patient groups at one and two years' are shown below:

	ONE-YEAR		TWO-YEAR	
SURVIVAL	CSA	AZA	CSA	AZA
PATIENT	95%	90%	90%	79%
GRAFT	90%	74%	85%	72%

Clearly, differences are apparent among the two patient groups favoring CSA therapy.

Both infectious and noninfectious complications were higher among AZA-treated than CSA-treated patients. Overall, the incidence of complications was two times more frequent in the AZA + PRED group than in the CSA group. The most frequent side-effects induced by CSA therapy were hirsutism (57%) and nephrotoxicity (17%). The length of initial hospitalization was significantly reduced in the CSA group (13.4 ± 6.1 days) when compared with that of the AZA + PRED group (18.6 ± 9.2 days; $p < .05$).

The investigators did not observe an improvement in renal function following conversion to AZA. They, nonetheless, concluded that "... the strategy of a short course of CSA followed by conversion to AZA + PRED seems to be safe and provides an overall increase of 15 percent in patient and graft survival when compared with a matched control group."

A final report to be reviewed here was published by the Innsbruck group (see Spielberger et al., 1988:169). Between February 1983 and September 1985, 68 consecutive patients receiving a cadaver kidney were randomly allocated to either continue CSA or to be switched to AZA and PRED at three months. Patients were between the ages of 14 and 60 years. Patients with diabetes, liver disease, and those who had not received at least two units of blood before transplantation were excluded from the study.

During the first three months following transplantation, 17.9 percent of the patients who were later converted, and 20 percent of the control group developed acute rejection. Over the entire follow-up period, 28.6 percent of the converted group suffered an acute rejection, in contrast to only 17.5 percent in the control group. All but two rejections after conversion proved to be reversible. In the control group, mild rejections occurred in seven patients between one and 168 weeks (mean, 109) after grafting. Two of these proved to be reversible, and five patients lost their grafts due to this complication.

Ten converted patients had to be switched back to CSA, eight for immunologic reasons and two because of hepatitis or severe steroid side-effects. Actuarial graft survival at four years was 91 percent in the converted group and 86.2 percent in the control group, taking three months posttransplant as a starting point. In all converted patients, a significant improvement in renal function occurred and was seen to continue for the entire observation period. While early CSA nephrotoxicity was found to be reversible within a short period, it took up to one year for other well-known CSA side-effects to disappear.

The authors concluded that "... for patients with otherwise intractable CSA nephrotoxicity, conversion to conventional immunosuppression can be recommended with a low risk of graft loss due to rejection. However, since some of the rejections were observed soon after conversion, CSA should probably not be discontinued abruptly but tapered slowly while compensating with AZA."

Discussion

The foregoing review of maintenance conversion studies yields very little by way of conclusion. As noted at the outset of the review, many of the studies concerned with conversion have been seriously deficient methodologically. Many of the studies are observational, and most of those that are randomized have inherent design flaws. Because the studies are often so vastly different, both in terms of design as well as content, conflicting results are not surprising. Nonetheless, this review does provide us with some helpful insights, and suggests some areas where there is consistency in research findings. Perhaps it is useful to consider these, after we have restated why conversion of immunosuppression holds some appeal, despite the results of the studies conducted thus far.

This review began by noting that there were many reasons for attempting to convert patients from immunosuppressive protocols that include cyclosporine to those that do not. The primary reasons are as follows:

- Chronic nephrotoxicity
- Chronic nonrenal toxicity (e.g., hepatotoxicity)
- Chronic immunologic tolerance
- Chronic rejection
- Oliogoanuria
- Interstitial fibrosis
- Life-threatening infection
- Lymphomas

- Hypertension
- Prolonged acute tubular necrosis
- Noncompliance with cyclosporine
- Convenience
- Cost

Clearly, there are many possible indications for conversion, some of which are little more than well-known side-effects associated with cyclosporine, upon which a further comment is required.

As noted earlier in this chapter, virtually every immunosuppressive agent has side-effects. In this regard, of the various agents, azathioprine is perhaps the safest in the long-term. The major side-effect associated with azathioprine is bone marrow depression. Prednisone has significant side-effects associated with its use. These are well-documented in the literature and include hypertension, obesity, diabetes, ocular disorders, and ischemic bone necrosis. Finally, the side-effects of cyclosporine can be of considerable consequence. These include: nephrotoxicity, hypertension, hepatotoxicity, leukopenia, slight bone marrow depression, lymphomas, hirsutism, and cost. In short, no immunosuppressive agent is entirely "safe", and, in this regard, a risk-benefit analysis is required to better determine which agents are best-indicated for which patients.

The literature suggests that there are several risk factors that may well undermine the efficacy of what we might refer to as "conversion therapy." These risk factors include: (1) cadaver grafts, (2) the use of antilymphocyte globulin, (3) diabetes, (4) regrafts, and (5) steroid resistant rejection. Although the literature is not consistent, particularly with respect to the appropriateness of conversion for cadaveric grafts, there do appear to be some relatively clear contraindications to conversion. Perhaps most noteworthy are the failed attempts to convert regrafted patients.

There are some clear benefits associated with conversion but, not surprisingly, there is also a downside. On the positive side, converted patients, when compared with CSA-treated patients, have better renal function, less hypertension, lower serum creatinine levels, and, ultimately, they save money in a direct sense for drugs. On the negative side, converted patients are more likely to have a greater propensity for acute rejection, a higher rate of graft loss, more "breakthrough" rejections, more serum infections, particularly if ALG is used, as well as a higher incidence of leukopenia, hepatic dysfunction, and infection. These problems are of major significance.

Finally, based on published accounts, it is apparent that conversion can be reasonably well accomplished in patients, provided they have a stable primary graft. Also, there appears to be some merit in the therapeutic overlap of immunosuppressive agents during the time when cyclosporine is being discontinued. However, even given these considerations, it is difficult to arrive at a definitive conclusion concerning the merits of conversion. As alluded to above, there are both risks and benefits associated with conversion. The more well-designed conversion studies suggest that the risks may outweigh the benefits at the present time. Caution is in order and, unfortunately, it does not appear that a large prospective multicenter trial of conversion is likely to be undertaken that will fully evaluate both the long-term and short-term consequences of conversion. Based upon current practices within the renal transplant community, it, therefore, does not seem prudent to pursue conversion as a routine policy. Instead, for patients who have developed complications associated with cyclosporine therapy, conversion may represent the only reasonable alternative available. In short, conversion may well be best applied as a "last ditch" effort to save a graft although, over time, economics may play an ever increasingly important role in the implementation of conversion policies.

Conclusion

This lengthy chapter provides a comprehensive overview of clinical immunosuppression--the key to the success of transplantation. The chapter began by tracing developments in the field of transplant immunology, and included consideration of very recent progress that may well shape the future of transplantation. Because of the significance of cyclosporine, we discussed this agent at considerable length. Although cyclosporine is not a panacea, it does represent perhaps the most significant of achievements in the pharmacological management of transplant rejection. The problems associated with cyclosporine were highlighted in our discussion of the side-effects and complications of various immunosuppressive agents. As noted, tradeoffs must be made in the selection of an appropriate immunosuppressive protocol for any given patient. Understanding these protocols is essential to an analysis of the costs and benefits associated with the administration of various immunosuppressive agents and techniques. These were, of course, described at length in this chapter, and the various protocols have been graphically depicted. Finally, we considered the merits of conversion from one immunosuppressive protocol to another, although our attention was primarily focused on conversion from cyclosporine therapy to more conventional types of immunosuppressive agents.

Unfortunately, as is true of much of the field of immunology, there are more uncertainties than most people wish to tolerate. It is difficult, if not impossible, to arrive at straightforward unequivocal conclusions. There are seemingly too many unknowns. We do not know for certain, for example, whether routine conversion is a prudent policy for many or just a few patients. We do not know enough about the long-term complications associated with a lifetime of immunosuppression. Most disheartening, perhaps, is the fact that the results of studies conducted by seasoned investigators are at odds with each other. Do blood transfusions make a difference? Why is it that cyclosporine monotherapy was liberally followed in Europe, yet double-drug therapy was widely adopted in the United States? Moreover, why is it that, even when similar protocols are followed cross-nationally, the results vary from center to center?

In short, it seems odd to write a conclusion for a chapter when there is relatively little that can be said that is devoid of debate and controversy. We cannot arrive at succinct conclusion. This does not, however, detract from the objective of this chapter. The fact that we are unable to arrive at firm conclusions is important to know. Recognition of the limitations of what is known enables us to more appropriately qualify our results. The remainder of this report will fill a number of gaps in our current knowledge about the costs and outcomes of renal transplantation. While the results may not be generalizable to all renal transplant recipients, it will become clear that the results will have importance for a broad range of patients. Therefore, throughout the remainder of this report it is important to keep in basic principles and practices that today characterize transplant immunology and renal transplantation in particular. The knowledge imparted in this chapter is critical to a fuller appreciation of this report.

CHAPTER 4

SOCIODEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF KIDNEY TRANSPLANT RECIPIENTS

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CHAPTER 4 SOCIODEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF KIDNEY TRANSPLANT RECIPIENTS

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Introduction

As described in Chapter 2, data were collected on a total of 396 renal transplant patients from medical and hospital billing records and through a series of patient interviews. A Baseline Medical Records Data Abstraction Form was used to obtain information concerning the patient's medical history, the transplant procedure, donor characteristics, and transplant costs. A Baseline Medical Records Data Abstraction Form was completed for each of the 396 patients who were included in the study. In addition, a Baseline Patient Questionnaire was used to obtain information on the patient's health, family and social life, medical costs, overall quality of life, and experience with rehabilitation and social service agencies following transplant surgery. The Baseline Patient Questionnaire, which was administered 3 months after the surgery, was completed by a total of 272 patients (although partial baseline patient questionnaires were completed by 18 of these patients).

The purpose of this chapter is to provide a broad descriptive overview of renal transplant patients. Selected data from the two baseline forms are summarized in this chapter. The chapter is divided into two sections. The first section describes the sociodemographic characteristics of the transplant patients and the second section contains information regarding background medical characteristics. For the purposes of these and all other subsequent analyses, patients are grouped according to the initial immunosuppressive drug protocol of the center at which their surgery was performed. The two initial immunosuppressive drug protocol groups are: patients receiving cyclosporine and prednisone (CSA + PRED) and patients receiving azathioprine, prednisone and antilymphocyte globulin (AZA + PRED + ALG). The AZA + PRED + ALG group consists of patients who received transplants at the following three centers: University of California, San Francisco; Ohio State University; and University of Wisconsin. The CSA + PRED groups consists of patients who received transplants at the University of Pittsburgh and the University of Texas, Houston.

Sociodemographic Characteristics

Age, Sex, and Racial Characteristics

The age distribution of renal transplant recipients included in the study is shown in Table 4-1. The distribution of patients by sex and race is presented in Table 4-2. Patient ages at time of transplant ranged from a minimum of 18.23 to a maximum of 66.97 years. The mean age of transplant recipients in the study population is 42.19 years (S.D.=11.91). Of the 396 participating renal transplant recipients, the majority are white (73.2%) and male (61.6%).

National data for patients transplanted in 1986 are summarized in Tables 4-3 and 4-4. The age distribution of participating transplant recipients is very similar to the United States Medicare eligible kidney transplant population. The mean age of cadaveric graft recipients in this study is 42.2 years compared with 41.7 years nationally. The sex distribution of patients is similar in both the transplant recipient population, as well as in this multicenter study. However, the percentage of black recipients is considerably lower in our study compared with what it is nationally (16.4% vs. 22.6%).

Few differences in the characteristics of the two immunosuppressive drug protocol groups can be observed. There is no difference between the average age of the two groups. The AZA + PRED + ALG group consists of a slightly

Table 4-1
Age Distribution of Participating Transplant Recipients*

Age (in Years)	All Patients	Primary Renal Diagnosis: Nondiabetes	Primary Renal Diagnosis: Diabetes	Initial Immunosuppressive Protocol: AZA + PRED + ALG	Initial Immunosuppressive Protocol: CSA + PRED
18.00 - 19.99 (%)	1.8	2.4	0.0	1.6	2.1
20.00 - 24.99 (%)	7.8	10.0	1.9	8.6	6.4
25.00 - 29.99 (%)	5.1	4.5	7.6	5.9	4.3
30.00 - 34.99 (%)	14.9	13.1	20.0	13.7	17.1
35.00 - 39.99 (%)	15.2	12.4	22.9	14.5	16.4
40.00 - 44.99 (%)	14.9	12.0	22.9	16.4	12.1
45.00 - 49.99 (%)	11.1	11.7	9.5	10.9	11.4
50.00 - 54.99 (%)	10.6	11.3	8.6	10.9	10.0
55.00 - 59.99 (%)	12.2	14.1	6.7	13.3	10.0
60.00 - 64.99 (%)	5.6	7.6	0.0	3.5	9.3
65 or more (%)	0.8	1.0	0.0	0.8	0.7
Range	18.23 - 66.97	18.23 - 66.97	20.25 - 58.86	18.23 - 66.97	18.85 - 65.73
Mean	42.19	42.9	40.1	41.94	42.55
S.D.	11.91	12.81	8.71	11.75	12.27

*Age at time of transplant

Table 4-2
Sex and Racial Distribution of Participating Transplant Recipients

	All Patients	Primary Renal Diagnosis		Initial Immunosuppressive Protocol	
		Nondiabetes	Diabetes	AZA + PRED + ALG	CSA + PRED
Sex					
Male (%)	61.6	62.5	59.0	63.3	58.6
Female (%)	38.4	37.5	41.0	36.7	41.4
Race					
White (%)	73.2	68.4	86.7	72.7	74.3
Black (%)	16.4	19.9	6.7	13.3	22.1
Asian (%)	5.8	7.2	1.9	8.2	1.4
Hispanic (%)	3.8	3.8	3.8	5.5	0.7
Native American (%)	0.8	0.7	1.0	0.4	1.4

Table 4-3
Age Distribution of 1986 U.S. Medicare-Eligible Kidney Transplant Recipients*

Age (in Years)	All Patients	Primary Renal Nondiabetes	Diagnosis Diabetes
18.00 - 19.99 (%)	1.5	1.9	0.3
20.00 - 24.99 (%)	6.6	7.5	3.1
25.00 - 29.99 (%)	9.9	9.3	12.3
30.00 - 34.99 (%)	14.3	12.8	19.9
35.00 - 39.99 (%)	14.9	13.4	20.6
40.00 - 44.99 (%)	13.6	13.0	15.9
45.00 - 49.99 (%)	12.8	13.2	11.0
50.00 - 54.99 (%)	11.1	11.8	8.4
55.00 - 59.99 (%)	8.6	9.4	6.0
60.00 - 64.99 (%)	4.7	5.5	1.7
65 or more (%)	1.9	2.2	0.8
Range	18.0 - 74.8	18.0 - 74.8	18.4 - 67.9
Mean	41.7	42.2	39.8
S.D.	11.4	12.0	9.8

*For cadaveric kidney transplant patients 17 years of age or older.
Source: Eggers, Health Care Financing Administration, 1989.

Table 4-4
Sex and Racial Distribution of 1986 U.S. Medicare-Eligible Kidney Transplant Recipients*

	All Patients	Primary Renal Diagnosis	
		Nondiabetes	Diabetes
Sex			
Male(%)	63.6	63.1	65.3
Female (%)	36.4	36.9	34.7
Race			
White (%)	73.9	71.2	83.7
Black (%)	22.6	24.9	14.4
Asian (%)	2.2	2.6	0.9
Native American (%)	0.8	0.9	0.7
Other/Unknown	0.4	0.5	0.4

*For cadaveric kidney transplant patients 18 years of age or older.
Source: Eggers, Health Care Financing Administration, 1989.

lower percentage of females than the CSA + PRED group. Although the proportion of the patients who are nonwhite does not vary between the two drug protocol groups, the racial composition of the two groups does differ somewhat. As can be seen in Table 4-2, the percentage Black is higher in the CSA + PRED group and the percentages Asian and Hispanic are higher in the AZA + PRED + ALG group. This difference, however, is not surprising given the specific centers that comprise the two groups.

With respect to primary renal diagnosis, the mean age of nondiabetic patients is slightly higher than that of the diabetic patients in the study. Diabetic patients, on the other hand, are more likely to be female and white compared with the nondiabetic patient group.

Marital Status and Household Composition

Of the 272 patients who completed the baseline patient questionnaire, the majority of patients were married three months posttransplant. As is shown in Table 4-5, the distribution of patients by marital status is as follows: 64.3 percent married, 2.6 percent widowed, 9.9 percent divorced, 4.4 percent separated, and 18.7 percent never married. Less than 10 percent of all patients (9.9%) reported that they lived alone.

Educational Attainment

The levels of education attained by the transplant recipients who completed the baseline patient questionnaire are shown in Table 4-6. The mean number of years of education among transplant recipients is 12.78 (S.D.=2.89). When asked about the highest degree obtained, 19.7 percent of patients reported that they never graduated from high school, 57.7 percent

Table 4-5
Marital Status of Participating Transplant Recipients Three Months Following Transplant Surgery

	All Patients	Primary Renal Diagnosis		Initial Immunosuppressive Protocol	
		Nondiabetics	Diabetes	AZA + PRED + ALG	CSA + PRED
Married (%)	64.3	64.0	65.2	63.2	66.7
Widowed (%)	2.6	3.0	1.4	3.8	0.0
Divorced (%)	9.9	7.4	17.4	10.3	9.2
Separated (%)	4.4	4.9	2.9	3.2	6.9
Never Married (%)	18.7	20.7	13.0	19.5	17.2

Table 4-6
Levels of Education Attained by Participating
Transplant Recipients

Years of Education	All Patients	Primary Renal Diagnosis		Initial Immunosuppressive Protocol	
		Nondiabetes	Diabetes	AZA + PRED + ALG	CSA + PRED
8 or Less (%)	7.4	8.9	2.9	7.0	8.0
9 - 12 (%)	53.3	54.2	50.7	55.1	49.4
13 - 16 (%)	30.5	26.1	43.5	28.1	35.6
17 - 18 (%)	6.3	7.9	1.4	7.0	4.6
19 or More (%)	2.6	3.0	1.4	2.7	2.3
Range	0.0 - 25.0	0.0 - 25.0	7.0 - 19.0	0.0 - 25.0	5.0 - 24.0
Mean	12.78	12.71	12.99	12.70	12.95
S.D.	2.89	3.06	2.35	2.93	2.82

had received a high school diploma, 18.0 percent had received a college or university degree, and 5.5 percent had received an advanced degree. The average number of years of education completed does not vary by primary renal diagnosis or initial immunosuppressive protocol.

Income and Net Worth

Patients were asked to estimate their total family income from all sources in 1985. The following sources of income were listed on the questionnaire: (1) your wages and/or salary; (2) spouses wages and/or salary; (3) income from pensions, social security, disability benefits; and (4) income from all other sources. Table 4-7 shows the income distribution of the patients who completed the Baseline Questionnaire. Of the 272 patients who responded to the Patient Baseline Questionnaire, 22 (8.1%) refused to disclose their income, and 11 (4.0%) indicated that they did not know or provided no response. As can be seen from the table, over one-half (127 of the 239 patients who provided income information) had 1985 household incomes of less than $20,000.

The net worth of patients was estimated by asking them to compare their total assets with their total debts, assuming they were to sell their cars, house, property and so forth and then pay off their debts. Taking the amount left, they were to add money they had in checking accounts, credit unions, stocks, and bonds. This total was then used as an approximation of their net worth. Once again, 18 patients refused to do this and 9 said that they did not know or provided no response. Table 4-8 summarizes the net worth of the 272 patients who completed a Patient Baseline Questionnaire. As is clearly shown in the table, the kidney transplant recipients who

Table 4-7
Total Household Income of Participating Transplant Recipients for 1985

Income Range	All Patients	Primary Renal Diagnosis		Initial Immunosuppressive Protocol	
		Nondiabetes	Diabetes	AZA + PRED + ALG	CSA + PRED
Less than $2,500 (%)	2.9	3.9	0.0	3.2	2.3
$2,500 - $4,999 (%)	8.8	8.9	8.7	9.2	8.0
$5,000 - $7,499 (%)	7.4	5.1	11.6	8.1	5.7
$7,500 - $9,999 (%)	8.1	7.9	8.7	8.1	8.0
$10,000 - $14,999 (%)	11.8	12.3	10.1	11.4	12.6
$15,000 - $19,999 (%)	7.7	5.9	13.1	6.5	10.3
$20,000 - $24,999 (%)	7.0	5.9	10.1	7.6	5.7
$25,000 - $29,999 (%)	8.5	6.9	13.1	7.0	11.5
$30,000 - $39,999 (%)	12.1	12.8	10.1	12.4	11.5
$40,000 - $74,999 (%)	9.2	9.9	7.2	10.8	5.7
$75,000 or More (%)	4.4	5.9	0.0	4.3	4.6
Refused (%)	8.1	9.4	4.3	7.0	10.3
No Response/ Don't Know (%)	4.0	4.4	2.9	4.3	3.4

Table 4-8
Estimated Net Worth of Participating Transplant Recipients

	All Patients	Primary Renal Diagnosis		Initial Immunosuppressive Protocol	
		Nondiabetes	Diabetes	AZA + PRED + ALG	CSA + PRED
Less than $10,000 (%)	43.0	41.9	46.4	43.2	42.5
$20,000 - $24,999 (%)	11.4	10.8	13.0	10.3	13.8
$25,000 - $49,999 (%)	12.5	12.8	11.6	13.5	10.3
$50,000 - $99,999 (%)	10.7	9.9	13.0	11.4	9.2
$100,000 - $199,999 (%)	6.6	6.9	5.8	5.4	9.2
$200,000 or more (%)	5.9	7.4	1.4	6.5	4.6
Refused (%)	6.6	5.9	8.7	6.5	6.9
No Response/ Don't Know (%)	3.3	4.5	0.0	3.2	3.4

participated in the study have few assets--43 percent of the patients have a net worth of less than $10,000.

Background Medical Characteristics

Primary Renal Diagnosis

Table 4-9 shows the primary renal disease diagnosis of the 396 renal transplant recipients who agreed to participate in the study. The diagnoses were obtained through a review of the patients' medical and hospital records. Diabetic nephropathy, glomerulonephritis, and hereditary-congenital disorders (largely polycystic kidney disease) are the most commonly reported diagnoses. As can be seen from the table, diabetic nephropathy is the primary renal diagnosis of over one-fourth of all patients. The primary diagnosis is undetermined in 14.4 percent of all patients. National data on primary renal disease for patients receiving kidney transplants in 1985 are as follows: diabetes, 18 percent; glomerulonephritis, 32 percent; hypertension, 13 percent; and other or unknown, 37 percent (see Eggers, 1988:223).

It is interesting to note that differences do exist in the primary renal diagnoses of the two immunosuppressive drug protocol groups. As is shown in Table 4-9, the AZA + PRED + ALG group has higher percentages of patients with diabetic nephropathy and other systemic diseases, as well as a higher percentage of patients with collagen-vascular diseases and acquired renal diseases, compared with the CSA + PRED group. The percentage of patients whose renal diagnosis was reported as undetermined is also higher in the AZA + PRED + ALG patient group. The CSA + PRED patient group has correspondingly higher percentages of patients with glomerulonephritis,

Table 4-9
Primary Renal Diagnosis of Participating Transplant Recipients*

Primary Renal Diagnosis	All Patients	Primary Renal Diagnosis		Initial Immunosuppressive Protocol	
		Nondiabetes	Diabetes	AZA + PRED + ALG	CSA + PRED
Glomerulonephritis (%)	22.5	30.6	0.0	19.1	28.6
Vascular Disorders (%)	8.3	11.3	0.0	5.9	12.9
Tubulo Interstitial Diseases (%)	7.1	9.6	0.0	5.9	9.3
Hereditary-Congenital Disorders (%)	15.9	21.6	0.0	15.6	16.4
Diabetic Nephropathy (%)	26.5	0.0	100.0	28.5	22.9
Other Systemic Diseases (%)	0.3	0.3	0.0	0.4	0.0
Collagen-Vascular Diseases (%)	4.3	4.8	0.0	5.1	2.9
Acquired Renal Diseases (%)	0.8	1.0	0.0	1.2	0.0
Undetermined (%)	14.4	19.6	0.0	18.4	7.1

*Percentages may not sum to 100.0 due to rounding error.

vascular disorders, tubulo-interstitial diseases, and hereditary-congenital disorders than the AZA + PRED + ALG group.

Length of Time Between Diagnosis of ESRD and Transplantation

As shown in Table 4-10, there is considerable variation in the length of time from the diagnosis of kidney disease to the time of transplant.[1] Among the 396 patients included in the study, the time between diagnosis and transplant varies from .21 to 39.78 years. The mean number of years is 6.89 years (S.D.=7.81). The length of time from initial diagnosis to transplant was greater for those in the AZA + PRED + ALG group (7.52 years) compared with those in the CSA + PRED group (5.73 years). With respect to primary renal diagnosis, the difference is greater. The mean length of time between diagnosis and transplant was 7.65 years for nondiabetic patients and 4.6 years for diabetic patients.

Previous ESRD Treatment Modalities

Each patient's medical record was examined and information was obtained regarding all other modalities that the patient was on since he or she began treatment for renal failure. Most patients in the study (75.5%) have been on only one other treatment modality prior to their transplant surgery. Only 66 patients (16.7%) have been on two previous modalities, while none had been on more than two previous modalities. A total of 31 patients (7.8%) were not on any other treatment modality prior to transplantation.

---

[1] It should be noted that this is the length of time between diagnosis of the patient's renal condition and transplantation, not the length of time between the beginning of dialysis and transplantation.

Table 4-10
Length of Time From the Diagnosis of Kidney Disease to the Time of Transplant Surgery

Length of Time (in Years)	All Patients	Primary Renal Diagnosis Nondiabetes	Primary Renal Diagnosis Diabetes	Initial Immunosuppressive Protocol AZA + PRED + ALG	Initial Immunosuppressive Protocol CSA + PRED
.01 - .99 (%)	15.6	11.8	30.0	16.6	13.8
1.00 - 1.99 (%)	17.4	15.7	22.1	17.8	16.7
2.00 - 2.99 (%)	11.0	8.7	17.3	8.3	15.9
3.00 - 3.99 (%)	10.5	10.5	10.6	8.3	14.5
4.00 - 4.99 (%)	5.4	5.9	4.8	6.3	4.3
5.00 - 9.99 (%)	16.4	20.6	4.8	15.8	17.4
10.00 - 14.99 (%)	7.9	9.4	3.8	7.9	8.0
15.00 - 24.99 (%)	11.5	13.2	6.7	13.8	7.2
25.00 or More (%)	4.1	4.2	3.8	5.1	2.2
Range	.21 - 39.78	.21 - 39.78	.29 - 35.28	.22 - 39.78	.21 - 31.43
Mean	6.89	7.65	4.76	7.52	5.73
S.D.	7.81	7.92	7.07	8.42	6.37

The previous treatment modalities of participating transplant recipients are shown in Table 4-10. Clearly, the most commonly reported previous modality is in-center hemodialysis, with 81.6% of the patients having been on in-center hemodialysis at some time before they received their transplant. Among the patients included in the study, continuous ambulatory peritoneal dialysis (CAPD) was the next most common previous treatment modality, with 26.3% of the patients having been on CAPD. Only three patients had been on home hemodialysis and one patient had been on intermittent peritoneal dialysis (IPD).

There were few differences in the previous treatment modalities of participating recipients when the two initial immunosuppressive protocol groups were compared, however, with respect to primary renal diagnosis, some differences are apparent. As can be seen in Table 4-11 diabetic patients are more likely to have been on CAPD and less likely to have been on in-center hemodialysis than are nondiabetic patients. Diabetic patients are also more likely than nondiabetic patients to have been on no previous treatment modalities.

Comorbidity Prior to Transplantation

Comorbidity among organ transplant recipients is an important consideration both before and following transplant surgery (Belzer, 1979:267; Bennett, 1988:433; Birkeland, 1983:1070; Blohme and Brynger, 1985:23; Boudreaux _et al_., 1987:376; Burns, 1982:170; Crosnier, 1981:232; Dummer _et al_., 1983:259; Editorial, 1984:601; 1985:965; Grenfell _et al_., 1986:1500; Grunfeld _et al_., 1975:391; Holzer _et al_., 1985:315; Ibels _et al_., 1978:25; Kahan _et al_., 1987:197; Kay, 1983:1099; Kenzora and Tilney, 1982:147; Kinlen _et al_.,

Table 4-11
Previous Treatment Modalities of Participating
Transplant Recipients

Treatment Modality	All Patients	Primary Renal Diagnosis		Initial Immunosuppressive Protocol	
		Nondiabetes	Diabetes	AZA + PRED + ALG	CSA + PRED
Home Hemodialysis (%)	0.8	1.0	0.0	1.2	0.0
In-Center Hemodialysis (%)	81.6	86.9	66.7	83.6	77.9
CAPD (%)	26.3	21.6	39.0	25.8	27.1
IPD (%)	0.3	0.3	0.0	0.4	0.0
None (%)	7.8	6.9	10.5	7.8	7.9

1983:1039; Lorber et al., 1987:35; Murray, 1973:57; Penn, 1978:492; 1979:1047; 1982:71; 1983:2790; 1983:1079; 1984:492; 1987:32; 1988:276; 1988:439; Peters et al., 1984:514; Prompt et al., 1985:672; Robitaille et al., 1985:1297; Rodenburg et al., 1985:122; Ruben et al., 1981:405; Salaman, 1983:118; Tellis et al., 1988:423; Tilney, 1982:184; Tilney and Luzarus, 1982:98: 1982:113; Tolkoff-Rubin and Rubin, 1988:554; Wyn et al., 1988:329) In general, severe comorbidity prior to surgery may be considered a contraindication to transplantation. However, comorbidity may also occur following transplant surgery, as a side-effect of the patient's immunosuppressive therapy. In this study we collected information regarding comorbidity both before and after transplantation. In this section we examine comorbidity prior to transplant surgery. The presence of comorbid conditions following transplantation is examined in a later chapter of this report.

Patients' medical records were reviewed to obtain information on whether or not patients had specific conditions prior to transplantation (cardiovascular disease, pulmonary disease, hepatic disease, juvenile onset diabetes mellitus, adult onset diabetes mellitus and cancer). The total number of comorbid conditions reported among the participating recipients is shown in Table 4-12. Among all patients included in the study, 41.4 percent had none of the specified comorbid conditions prior to transplantation, while 42.9 percent had only one condition and 14.9 percent had two conditions. Since adult onset diabetes and juvenile onset diabetes are two of the comorbid conditions specified, it is not surprising to note that patients in the diabetes patient group have more comorbid conditions than patients in the nondiabetic group.

Table 4-12
Total Number of Comorbid Conditions of Participating
Transplant Recipients Prior To Transplantion

Number of Comorbid Conditions	All Patients	Primary Renal Diagnosis		Initial Immunosuppressive Protocol	
		Nondiabetes	Diabetes	AZA + PRED + ALG	CSA + PRED
0 Conditions (%)	41.4	56.4	0.0	43.4	37.9
1 Condition (%)	42.9	39.2	53.3	37.9	52.1
2 Conditions (%)	14.9	3.4	46.7	18.0	9.3
3 Conditions (%)	0.5	0.7	0.0	0.4	0.7
4 Conditions (%)	0.3	0.3	0.0	0.4	0.0

As can be seen in Table 4-13, prior to transplant surgery over 40 percent of the patients had cardiovascular disease. The next most commonly reported condition was juvenile onset diabetes mellitus (16.2%), followed by adult onset diabetes mellitus (11.9%). In contrast, very few patients had pulmonary disease, hepatic disease, or cancer prior to transplantation. In terms of differences in comorbidity between the two patient groups, a higher percentage of patients in the AZA + PRED + ALG group were reported to have adult onset diabetes and a lower proportion of patients were reported to have cardiovascular disease compared with patients in the CSA + PRED group. Not surprisingly, nondiabetic patients were less likely to have juvenile onset diabetes and adult onset diabetes than were those in the diabetic patient group. Those in the diabetic patient group were also somewhat more likely to have cardiovascular disease than were those in the nondiabetic group.

Information concerning the presence of comorbid conditions prior to transplantation was also obtained from the Baseline Patient Questionnaire. Patients were given a lengthy list of conditions and asked to indicate which, if any, they had before their transplant. Not surprisingly, the most commonly reported condition was chronic kidney disorder. The next most prevalent comorbid conditions reported by kidney transplant patients include: (1) hypertension (74.5%), (2) vision disorders (53.7%), (3) sleep disorders (42.4%), (4) diabetes (26.1%), and (5) nervous or emotional problems (25.5%).

Medications Prescribed Just Prior to Transplantation

The medical records of patients were also abstracted to determine which medications were prescribed for transplant recipients just prior to surgery.

Table 4-13
Comorbidity of Participating Transplant Recipients At Time of Transplant

	All Patients	Primary Renal Diagnosis		Initial Immunosuppressive Protocol	
		Nondiabetes	Diabetes	AZA + PRED + ALG	CSA + PRED
Cardiovascular Disease (%)	41.9	39.9	46.7	37.9	48.6
Pulmonary Disease (%)	3.0	4.1	0.0	4.3	0.7
Hepatic Disease (%)	1.5	2.1	0.0	2.0	0.7
Juvenile Onset Diabetes (%)	16.2	0.3	61.0	16.0	17.1
Adult Onset Diabetes (%)	11.9	2.1	39.0	15.2	5.7
Cancer (%)	0.8	1.0	0.0	1.2	0.0

As shown in Table 4-14, antihypertensive medication was being prescribed for over half (51.5%) of all patients. Also, steroids were being prescribed for 44.4 percent of the patients included in the study. However, Table 4-14 reveals considerable variation in the medications prescribed to patients from the two initial immunosuppressive drug protocol groups. Patients in the AZA + PRED + ALG group were much more likely than patients in the CSA + PRED group to be taking antihypertensive, cardiotonic and antiinflammatory (non-steroid) medications just prior to their transplant surgery. Patients in the CSA + PRED group, on the other hand, were much more likely to be taking antiinflammatory (steroid) medications.

Level of Disability Prior to Transplantation

Finally, a member of the transplant center staff who was familiar with each patient was asked to evaluate the level of disability of the recipient just prior to transplant surgery. Patient disability prior to transplantation, as reported by transplant center staff, is summarized in Table 4-15 for all patients, as well as for patients grouped by initial immunosuppressive protocol. similar information for patients grouped by primary renal diagnosis is presented in Table 4-16. Only 3.8 percent of all transplant patients were considered to have a complete physical and/or mental disability. However, over half (56.1%) were considered to have a significant but not complete physical and/or mental disability. In this category most were reported to be unable to work or attend school. Only 34.9 percent of the patients included in the study were considered to have a slight or no physical and/or mental disability.

Table 4-14
Medications Prescribed Just Prior to Transplant Surgery

Medications	All Patients	Primary Renal Diagnosis		Initial Immunosuppressive Protocol	
		Nondiabetes	Diabetes	AZA + PRED + ALG	CSA + PRED
Antihypertensive (%)	51.5	50.2	55.2	64.1	28.6
Antiarrhythmic (%)	1.5	1.4	1.9	2.0	0.7
Cardiotonic (%)	7.6	7.9	6.7	10.9	1.4
Antiinflammatory (Steroid) (%)	44.4	46.7	39.0	32.4	67.1
Antiinflammatory (Non-Steroid) (%)	8.1	7.9	8.6	12.5	0.0
Anticonvulsive (%)	2.3	2.4	1.9	3.5	0.0

Table 4-15
Level of Disability of Participating Transplant Recipients Just Prior to Transplant Surgery as Reported by Transplant Center Staff, Overall and by Initial Immunosuppressive Protocol

Level of Disability	All Patients	Initial Immunosuppressive Protocol AZA + PRED + ALG	CSA + PRED
Complete physical and/or mental disability; patient hospitalized or essentially at home (%)	3.8	2.3	6.4
Significant but not complete physical and/or mental disability			
- patient unable to work or attend school (%)	37.4	34.4	42.9
- patient worked or attended school part-time (less than 50%) (%)	10.1	5.9	17.9
- patient worked or attended school essentially full-time (%)	8.6	4.3	16.4
Slight or no physical and/or mental disability			
- patient unable to work or attend school (%)	9.1	14.1	0.0
- patient worked or attended school part-time (less than 50%) (%)	3.3	3.5	2.9
- patient worked or attended school full-time but at a lower level of performance than at pre-illness (%)	4.8	5.9	2.9
- patient worked or attended school full-time at pre-illness level of performance (%)	12.9	15.2	8.6
- patient was physically and mentally able to work or attend school but chose not to (%)	3.0	3.5	2.1
- patient was physically and mentally able to work but was unable to find work (%)	0.8	1.2	0.0
- unknown (%)	1.0	1.6	0.0
Unknown (%)	5.3	8.1	0.0

Table 4-16
Level of Disability of Participating Transplant Recipients Just Prior to Transplant Surgery as Reported by Transplant Center Staff by Primary Renal Diagnosis

Level of Disability	Primary Renal Diagnosis Nondiabetes	 Diabetes
Complete physical and/or mental disability; patient hospitalized or essentially at home (%)	3.8	3.8
Significant but not complete physical and/or mental disability		
- patient unable to work or attend school (%)	32.3	51.4
- patient worked or attended school part-time (less than 50%) (%)	10.1	10.5
- patient worked or attended school essentially full-time (%)	8.6	8.6
Slight or no physical and/or mental disability		
- patient unable to work or attend school (%)	10.0	6.7
- patient worked or attended school part-time (less than 50%) (%)	4.5	0.0
- patient worked or attended school full-time but at a lower level of performance than at pre-illness (%)	4.1	6.7
- patient worked or attended school full-time at pre-illness level of performance (%)	15.8	4.8
- patient was physically and mentally able to work or attend school but chose not to (%)	3.8	1.0
- patient was physically and mentally able to work but was unable to find work (%)	1.0	0.0
- unknown (%)	1.0	0.0
Unknown (%)	4.8	6.7

It is particularly interesting to note the tremendous differences that exist between the two immunosuppressive drug protocol groups with respect to the evaluation of patient disability by the transplant center staff. Among the AZA + PRED + ALG group only 2.3 percent of the patients were considered to have a complete physical and/or mental disability and 44.6 percent of the patients were considered to have a significant but not complete physical and/or mental disability. Among the CSA + PRED group the percentages of patients with complete physical and/or mental disabilities and significant but not complete physical and/or mental disabilities were 6.4 percent and 77.2 percent, respectively. For the AZA + PRED + ALG group, 45.0 percent of the patients were considered to have a slight or no disability, compared with only 16.5 percent of the CSA + PRED group. Since neither data obtained from the patients' medical records nor data provided by patients themselves indicate that patients in the CSA + PRED group are more disabled than patients in the AZA + PRED + ALG group, it is likely that the large differences reported in Table 4-15 reflect the perceptions of the transplant center staff.

With respect to primary renal diagnosis, there is no difference in the two groups with respect to the percentages of patients who were considered to have a complete physical and/or mental disability. However, as shown in Table 4-16, patients in the diabetic group were more likely than those in the nondiabetic group to have a significant but not complete physical and/or mental disability. The difference between the two groups was most pronounced in terms of the percentage of patients with a significant but not complete disability who were reported as unable to work or attend school.

Discussion

This chapter briefly highlights key sociodemographic and clinical characteristics of patients according to their initial immunosuppressive protocol and primary renal diagnosis. As is apparent, there are relatively few differences between the various groups. Moreover, in terms of the demographic and diagnostic variables, the patients in the current study are similar to the national profile of patients transplanted in 1986 in the United States. While there are considerable differences between the two immunosuppressive protocol groups between the two primary renal diagnosis groups with respect to staff evaluation of the level of patient functioning, this will be analyzed further and discussed at great length in later chapters of the report.

CHAPTER 5

OPERATIVE PROCEDURES AND IMMUNOSUPPRESSIVE DRUG ADMINISTRATION

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Introduction

As discussed in detail in Chapter 3 there are major differences from one transplant center to another in the clinical management of renal transplant patients--in terms of the transplant surgery itself, as well as in the immunosuppressive drug protocol used following transplantation. In recent years, the differences that have received the most attention involve the combination of immunosuppressive drugs used initially, for maintenance, and for the treatment of episodes of rejection. For example, while virtually all patients receive cyclosporine, there is considerable variation across centers with respect to when cyclosporine is begun. At some centers patients initially receive cyclosporine and prednisone. For these patients, cyclosporine therapy is begun on the day of transplantation, or the day prior to surgery. Patients at other centers initially receive azathioprine, prednisone and antilymphocyte globulin (ALG). For these patients, cyclosporine may not be administered until several days posttransplant.

In the preceding chapter of this report, we presented a description of the sociodemographic and clinical characteristics of the 396 renal transplant patients included in this study. However, before beginning our examination of patient outcomes, it is perhaps equally important to examine differences in the clinical management of the patients both during their initial hospital stay and in the months following transplant surgery.

The purpose of this chapter is to provide a broad overview of the transplant surgery and the immunosuppressive drug protocols of the participating renal transplant recipients. The data presented in this chapter were obtained from two sources--the Baseline Medical Records Data Abstraction Form and the Follow-up Medical Records Information Forms. The

Baseline Medical Records Data Abstraction Form, which was completed by a data collector at the transplant center, was used to collect information concerning the transplant procedure and the patient's initial immunosuppressive treatment protocol. The Follow-up Medical Records Information Forms, which were completed at three-month intervals following transplant surgery, were used to obtain information regarding the maintenance doses of various immunosuppressive drugs being administered during the follow-up data collection period, as well as the doses of specific drugs used to treat episodes of rejection.

Our discussion is divided into three sections. The first section describes the transplant surgery. In the second section we present information regarding the initial or induction immunosuppressive protocols. The third section contains a summary of the immunosuppressive drugs administered from discharge to 15 months posttransplant. As in previous chapters, for the purpose of these analyses, patients are grouped according to the initial immunosuppressive drug protocol of the center at which their surgery was performed. The two initial immunosuppressive drug protocol groups are: patients receiving cyclosporine and prednisone (CSA + PRED) and patients receiving azathioprine, prednisone and antilymphocyte globulin (AZA + PRED + ALG). The AZA + PRED + ALG group consists of patients who received transplants at the following three centers: University of California, San Francisco; Ohio State University; and University of Wisconsin. The CSA + PRED group consists of patients who received transplants at the University of Pittsburgh and the University of Texas, Houston.

The Transplant Surgery

Table 5-1 presents a summary of the reported revascularization times of the 396 transplant procedures. Reported revascularization times ranged from a minimum of 0 minutes to a maximum of 65 minutes. The overall mean revascularization time was 25.3 minutes (S.D.= 14.4). The centers that initially administer AZA + PRED + ALG reported longer revascularization times than the centers that initially administer CSA + PRED. As can be seen from Table 5-1, the mean revascularization time reported for the AZA + PRED + ALG patient group was 28.7 minutes, compared with 18.6 minutes for the CSA + PRED patient group.

While the recipients were hospitalized for the transplant surgery, a splenectomy was performed on only two patients, thoracic duct drainage was performed on one patient, and one patient received total lymphoid irradiation. Endarterectomy was required in very few cases--either for the recipient (N=7) or in the case of the donor renal artery (N=2). In most cases only one arterial anastomosis was performed. Among the 396 transplant recipients included in the study, one arterial anastomosis was performed in 86.1 percent of the cases, two were performed in 12.9 percent of the cases and three were performed in only 0.5 percent of the cases. Patients' medical records were also examined to determine whether or not the recipient received blood transfusions at the time of the transplant. According to the medical records, 40.9 percent did receive transfusions at the time of transplant.

Information was also collected regarding whether or not the patient required dialysis following the transplant procedure. This information is summarized in Table 5-2. Of the 396 patients who were included in the study, 14 patients (3.5%) experienced a graft failure and returned to

Table 5-1
Revascularization Time, Overall and by Initial Immunosuppressive Protocol

	All Patients	Initial Immunosuppressive Protocol	
		AZA + PRED + ALG	CSA + PRED
Less than 10 Minutes (%)	7.6	0.4	20.7
10-14 Minutes (%)	7.8	8.6	6.4
15-19 Minutes (%)	18.2	21.5	12.1
20-24 Minutes (%)	18.7	21.1	14.3
25-29 Minutes (%)	6.3	1.6	15.0
30-39 Minutes (%)	21.2	19.9	23.6
40-49 Minutes (%)	12.1	17.6	2.1
50 Minutes or More (%)	5.6	8.6	0.0
Missing (%)	2.5	0.8	5.7
Range	0.0 - 65.0	5.0 - 65.0	0.0 - 40.0
Mean	25.3	28.7	18.6
S.D.	14.4	14.3	12.0

Table 5-2
Number of Days Dialysis Was Required Following Transplant Surgery, Overall and by Initial Immunosuppressive Protocol

Number of Days	All Patients	Initial Immunosuppressive Protocol	
		AZA + PRED + ALG	CSA + PRED
0 Days (%)	78.8	84.8	67.9
1-2 Days (%)	2.0	1.6	2.9
3-5 Days (%)	2.5	2.3	2.9
6-8 Days (%)	4.0	2.7	6.4
9-11 Days (%)	2.8	1.6	5.0
12-20 Days (%)	2.3	2.0	2.9
21-26 Days (%)	2.0	2.0	2.1
No Response (%)	1.0	0.4	2.1
Returned to maintenance dialysis prior to discharge	3.5	2.0	6.4
Died prior to discharge	1.0	0.8	1.4

maintenance dialysis during their initial hospital stay and four patients (1.0%) died prior to discharge from the hospital. Overall, 312 of the 396 patients (78.8%) did not require dialysis following the transplant procedure. For those patients who did require dialysis, the number of days that the recipient required dialysis ranged from one to 26 days. As shown in Table 5-2, patients in the AZA + PRED + ALG group were less likely than patients in the CSA + PRED group to require dialysis following transplantation.

Among the patients who were included in the study, there was considerable variation in the length of the hospital stay associated with the transplant surgery. The length of the initial hospital stay--computed from the date of admission to the date of discharge--for all patients in the study is summarized in Table 5-3. The length of stay ranged from a minimum of six days to a maximum of 252 days. Overall, the mean length of stay was 21.9 days. It is noteworthy that in 1986, the average length of stay for all Medicare cadaveric kidney transplant recipients (for those patients 18 years of age or older, receiving their first transplant) was 19.5 days (Eggers, Health Care Financing Administration, 1989).

Although the means do not differ for the two initial immunosuppressive protocol groups, patients in the CSA + PRED group were more likely to be discharged sooner than were patients in the AZA + PRED + ALG group. As can be seen in Table 5-3, 27.9 percent of CSA + PRED patients had an initial hospital stay of less than two weeks, compared with only 18.8 percent of AZA + PRED + ALG patients. However, a higher percentage of CSA + PRED patients spent 35 or more days in the hospital than did AZA + PRED + ALG patients. It is, of course, important to recognize that the maximum stay of 252 days tends to raise the mean length of stay for the CSA + PRED patient

Table 5-3
Length of Initial Hospital Stay of Participating Transplant Recipients Compared with 1986 Medicare Transplant Recipients

Number of Days	All Patients	Initial Immunosuppressive Protocol AZA + PRED + ALG	Initial Immunosuppressive Protocol CSA + PRED	1986 Medicare Transplant Patients*
Less than 7 Days(%)	1.5	0.8	2.9	2.2
7 - 13 Days (%)	19.9	18.0	25.0	35.8
14 - 20 Days (%)	28.0	27.3	30.0	27.8
21 - 27 Days (%)	31.8	35.9	24.3	15.9
28 - 34 Days (%)	7.3	8.2	5.7	8.1
35 or More Days (%)	11.4	9.8	12.1	10.1
Range	6.0 - 252.0	6.0 - 93.0	6.0 - 252.0	2.0 - 149.0
Mean	21.9	21.6	22.4	19.5
S.D.	15.8	10.4	22.6	13.6

* Information presented are for cadaveric transplant receipients, 18 years of age or older, receiving their first transplant.
Source: Paul Eggers, Health Care Financing Administration, 1989.

group. This is clearly reflected in the higher standard deviation for the CSA + PRED group.

Since, in many cases, a long length of stay may be associated with problems associated with the transplantation procedure, we examined the length of stay of patients by discharge status. Of the 396 patients included in the study, four patients were discharged dead, 14 patients were discharged with failed grafts, and 378 were discharged from the hospital with functioning grafts. For those patients who were discharged from the hospital with a functioning graft, the mean length of stay was 20.5 days (S.D.=9.4). However, for patients who experienced graft failures or died during their initial hospital stay, the mean length of stay was 50.9 days (S.D.=53.7). Interestingly, diabetic and nondiabetic patients did not vary in terms of the lengths of their initial hospital stays.

Initial Immunosuppression

Review of patients' medical records provided information regarding the initial or induction immunosuppressive protocols of patients participating in the study. In the case of 69 patients (17.4%) immunosuppression began one day prior to their transplant surgery, while for 325 patients (82.1%) it began on the day of surgery. In the case of two patients this information was unavailable. Table 5-4 shows the initial immunosuppressants that patients received. Prednisone or other steroids were received by 99.7 percent of all transplant recipients, while 61.4 percent received azathioprine and 63.6 percent received Minnesota ALG. Oral cyclosporine was received by 33.6 percent of patients and parenteral cyclosporine was administered to 12.4 percent of patients.

Table 5-4
Initial Immunosuppressants Received

Percent of Patients Receiving:	All Patients	Initial Immunosuppressive Protocol	
		AZA + PRED + ALG	CSA + PRED
Cyclosporine (Oral) (%) (Oral) (%)	33.6	0.0	95.0
Cyclosporine (Parenteral) (%)	12.4	0.0	35.0
Prednisone (or Other Steroid) (%)	99.7	99.6	100.0
Azathioprine (%)	61.4	99.2	1.4
Minnesota ALG (%)	63.6	98.4	0.0

As can be seen in the table, there is a very apparent difference in the initial immunosuppressive protocols of the five centers included in the study. Virtually all of the 256 patients who received their transplants at the University of California, Ohio State University, and the University of Wisconsin initially received azathioprine, prednisone and Minnesota ALG. In contrast, the 140 patients who received their transplants at the University of Pittsburgh and the University of Texas initially received cyclosporine and prednisone. Since grouping transplant patients by transplant center reflects their initial immunosuppressive protocol we continue to examine patients separately by these groups in our subsequent analysis of patient outcomes.

Most of the 396 patients included in the study (97.0%) began cyclosporine therapy at some time during their initial hospital stay. Table 5-5 presents information regarding when cyclosporine therapy was begun, for all patients as well as separately for the two initial immunosuppressive protocol groups. Of the 140 patients who initially received CSA + PRED, seven patients (5.0%) began one day prior transplantation and 133 patients (95.0%) began the day of the transplant. Among the patients who initially received AZA + PRED + ALG, cyclosporine was first administered from one to 35 days posttransplant, although for the majority cyclosporine therapy was begun between three and seven days following transplant surgery.

Initial doses of oral cyclosporine, parenteral cyclosporine, prednisone (or other steroid), azathioprine, and Minnesota ALG of patients in the two initial immunosuppressive protocol groups are shown in Table 5-6. The differences between the two groups are much as expected. Clearly, the patients in the study can be divided into two distinct groups: patients who initially receive

Table 5-5
When Cyclosporine Therapy Was Begun, Overall and by Initial Immunosuppressive Protocol

	All Patients	Initial Immunosuppressive Protocol	
		AZA + PRED + ALG	CSA + PRED
1 day prior to transplant	1.8	--	5.0
Day of transplant (%)	33.6	--	95.0
1 day posttransplant (%)	1.0	1.6	--
2 days posttransplant (%)	5.1	7.8	--
3 days posttransplant (%)	6.3	9.8	--
4 days posttransplant (%)	15.2	23.4	--
5 days posttransplant (%)	10.4	16.0	--
6-7 days posttransplant (%)	8.1	12.6	--
8-9 days posttransplant (%)	5.1	7.8	--
10-14 days posttransplant (%)	6.6	10.2	--
15-20 days post-transplant (%)	1.3	2.0	--
21 or more days post-transplant (%)	1.8	2.7	--
No response (%)	1.0	1.6	--
Did not begin cyclosporine therapy (%)	3.0	4.7	--

Table 5-6
Initial Doses of Various Immunosuppressive Drugs

	Initial Immunosuppressive Protocol	
Dose	AZA + PRED + ALG	CSA + PRED
Cyclosporine (Oral)		
0 Mg/Kg/Day (%)	100.0	5.0
5.0 - 11.9 Mg/Kg/Day (%)	-	7.2
12.0 - 13.9 Mg/Kg/Day (%)	-	12.9
14.0 - 15.9 Mg/Kg/Day (%)	-	20.0
16.0 - 17.9 Mg/Kg/Day (%)	-	13.6
18.0 - 19.9 Mg/Kg/Day (%)	-	16.4
20.0 - 24.9 Mg/Kg/Day (%)	-	14.3
25.0 or More Mg/Kg/Day (%)	-	10.7
Cyclosporine (Parenteral)		
0 Mg/Kg/Day (%)	100.0	65.0
1.0 - 1.9 Mg/Kg/Day (%)	-	2.9
2.0 - 2.4 Mg/Kg/Day (%)	-	11.4
2.5 - 2.9 Mg/Kg/Day (%)	-	15.0
3.0 or More Mg/Kg/Day (%)	-	5.7
Prednisone (or other steroid)		
Less than 2 Mg/Kg/Day (%)	30.1	2.9
2.0 - 3.9 Mg/Kg/Day (%)	39.1	3.6
4.0 - 5.9 Mg/Kg/Day (%)	29.7	1.4
6.0 - 9.9 Mg/Kg/Day (%)	1.2	20.0
10.0 - 13.9 Mg/Kg/Day (%)	-	28.6
14.0 - 17.9 Mg/Kg/Day (%)	-	29.3
18.0 or More Mg/Kg/Day (%)	-	14.3
Azathioprine		
0 Mg/Kg/Day (%)	5.9	98.6
0.1 - 1.9 Mg/Kg/Day (%)	7.4	0.7
2.0 - 2.9 Mg/Kg/Day (%)	9.4	0.7
3.0 - 3.9 Mg/Kg/Day (%)	12.9	-
4.0 - 4.9 Mg/Kg/Day (%)	29.7	-
5.0 - 5.9 Mg/Kg/Day (%)	15.2	-
6.0 or More Mg/Kg/Day (%)	19.5	-
Minnesota ALG		
0 Mg/Kg/Day (%)	1.6	100.0
0.1 - 3.9 Mg/Kg/Day (%)	34.4	-
4.0 - 9.9 Mg/Kg/Day (%)	3.1	-
10.0 - 11.9 Mg/Kg/Day (%)	5.1	-
12.0 - 13.9 Mg/Kg/Day (%)	8.6	-
14.0 - 15.9 Mg/Kg/Day (%)	5.9	-
16.0 - 19.9 Mg/Kg/Day (%)	16.0	-
20.0 or More Mg/Kg/Day (%)	25.4	-

cyclosporine and high dose steroids and patients who initially receive azathioprine, Minnesota ALG and low dose steroids.

As noted earlier, for the majority of the AZA + PRED + ALG patients included in our study, cyclosporine therapy was begun within a week following their transplant surgery. Of the 378 patients who were discharged from the hospital with functioning grafts, only 4.0 percent were not taking cyclosporine. Approximately 30 percent of the patients were taking azathioprine at the time of discharge, and all were taking prednisone or other steroids. Discharge doses of cyclosporine, prednisone (or other steroids), and azathioprine for all patients who were discharged from the hospital with a functioning graft are shown in Table 5-7. Data are presented for all patients, as well as separately for the two initial immunosuppressive protocol groups.

Examination of Table 5-7 indicates that the two initial immunosuppressive protocol groups continue to differ in the drug protocols used following discharge from the hospital. Most patients who initially received CSA + PRED continue receiving CSA + PRED following discharge (only 10% of the CSA + PRED group was receiving azathioprine at the time of discharge). Some of the patients who initially received AZA + PRED + ALG were receiving CSA + PRED at the time of discharge, while others were receiving azathioprine in addition to cyclosporine and prednisone. Approximately 40 percent of the patients who initially received AZA + PRED + ALG were receiving azathioprine at the time of discharge. However, as is shown in Table 5-7, there is considerable variation in the discharge doses of cyclosporine and prednisone for the two initial immunosuppressive protocol groups. Patients who initially received AZA + PRED + ALG had lower

Table 5-7
Discharge Doses of Various Immunosuppressive Drugs For Those Patients Discharged From The Hospital With A Functioning Graft

Dose	All Patients	Initial Immunosuppressive Protocol: AZA + PRED + ALG	Initial Immunosuppressive Protocol: CSA + PRED
Cyclosporine			
0 Mg/Kg/Day (%)	4.0	5.6	0.8
0.1-1.9 Mg/Kg/Day (%)	0.3	0.4	0.0
2.0-4.9 Mg/Kg/Day (%)	6.6	9.6	0.8
5.0-6.9 Mg/Kg/Day (%)	9.5	12.4	3.9
7.0-8.9 Mg/Kg/Day (%)	11.1	14.5	4.7
9.0-11.9 Mg/Kg/Day (%)	37.6	46.6	20.2
12.0-14.9 Mg/Kg/Day (%)	16.9	9.6	31.0
15.0-17.9 Mg/Kg/Day (%)	9.3	1.2	24.8
18.0-20.9 Mg/Kg/Day (%)	3.2	0.0	9.3
21.0 or more Mg/Kg/Day (%)	1.6	0.0	4.7
Prednisone (or other steroid)			
0.1-0.2 Mg/Kg/Day (%)	7.4	1.2	19.4
0.3 Mg/Kg/Day (%)	15.7	4.9	36.4
0.4 Mg/Kg/Day (%)	19.1	15.4	26.4
0.5 Mg/Kg/Day (%)	25.0	32.8	10.1
0.6 Mg/Kg/Day (%)	9.8	13.8	2.3
0.7 Mg/Kg/Day (%)	4.5	6.1	1.6
0.8 Mg/Kg/Day (%)	5.3	7.3	1.6
0.9 Mg/Kg/Day (%)	1.9	2.0	1.6
1.0 Mg/Kg/Day (%)	4.8	7.3	0.0
1.1-1.4 Mg/Kg/Day (%)	3.7	5.7	0.0
1.5 or more Mg/Kg/Day (%)	2.7	3.6	0.8
Azathioprine			
0 Mg/Kg/Day (%)	69.8	59.4	89.9
0.1-0.5 Mg/Kg/Day (%)	4.0	5.6	0.8
0.6-0.8 Mg/Kg/Day (%)	6.3	6.4	5.4
0.9-1.1 Mg/Kg/Day (%)	9.5	13.3	2.3
1.2-1.4 Mg/Kg/Day (%)	4.8	6.8	0.8
1.5-1.7 Mg/Kg/Day (%)	2.9	4.4	0.0
1.8 or more Mg/Kg/Day (%)	2.6	3.6	0.8

discharge doses of cyclosporine and higher discharge doses of steroids than patients who initially received CSA + PRED.

Immunosuppression During Follow-up

As described earlier, a Follow-up Medical Records Form was used to collect information regarding the immunosuppressive protocol of patients in the months following transplantation. The first follow-up medical records data collection form covered the period from hospital discharge until three-months posttransplant. All other follow-up periods were of a three-month duration, unless the patient was withdrawn from the study during the follow-up period (for example, if the recipient died or experienced a graft failure).

Information regarding the immunosuppressive protocols of patients at the beginning of the three-month follow-up period (i.e., at the time of hospital discharge), and at 3 months, 6 months, 9 months, and 12 months posttransplant is summarized in Tables 5-8 through 5-12, respectively. Each table presents the number and percentage of patients who were receiving CSA only, PRED only, CSA + PRED, CSA + AZA, AZA + PRED, and CSA + AZA + PRED, for all patients as well as for the two initial immunosuppressive protocol groups. The tables do not contain an AZA only group because no patient was reported to be receiving azathioprine and no other immunosuppressive drug. Each table also presents the mean drug dosages of CSA, PRED, and AZA (in Mg/Kg/Day) for each of the six drug protocol groups.

Table 5-8 shows that at the beginning of the three-month follow-up data collection period (i.e., at the time of discharge from the hospital), the vast majority of the patients in the study were receiving either CSA + PRED

Table 5-8
Immunosuppressive Protocol at Beginning of the Three Month Follow-up Period, Overall and by Initial Immunosuppressive Protocol

	Initial Immunosuppressive Protocol				All Patients		Mean Drug Dosage (Mg/Kg/Day)		
	AZA + PRED + ALG		CSA + PRED				CSA	PRED	AZA
	Number	Percent	Number	Percent	Number	Percent			
CSA Only	-	-	4	3.2	4	1.1	8.8	-	-
PRED Only	4	1.6	1	0.8	5	1.3	-	.72	-
CSA + PRED	134	54.5	107	85.6	241	65.0	12.2	.52	-
CSA + AZA	-	-	-	-	-	-	-	-	-
AZA + PRED	12	4.9	-	-	12	3.2	-	.74	1.4
CSA + AZA + PRED	96	39.0	13	10.4	109	29.4	7.7	.51	1.0

Table 5-9
Immunosuppressive Protocol Three Months Posttransplant, Overall and by Initial Immunosuppressive Protocol

	Initial Immunosuppressive Protocol				All Patients		Mean Drug Dosage (Mg/Kg/Day)		
	AZA + PRED + ALG		CSA + PRED				CSA	PRED	AZA
	Number	Percent	Number	Percent	Number	Percent			
CSA Only	-	-	5	4.3	5	1.4	6.6	-	-
PRED Only	2	0.8	1	0.9	3	0.9	-	.67	-
CSA + PRED	119	50.2	86	74.8	205	58.2	8.1	.30	-
CSA + AZA	-	-	1	0.9	1	0.4	4.8	-	1.8
AZA + PRED	8	3.4	1	0.9	9	2.6	-	.37	1.1
CSA + AZA + PRED	108	45.6	21	18.3	129	36.6	5.5	.31	0.9

Table 5-10
Immunosuppressive Protocol Six Months Posttransplant, Overall and by Initial Immunosuppressive Protocol

	Initial Immunosuppressive Protocol				All Patients		Mean Drug Dosage (Mg/Kg/Day)		
	AZA + PRED + ALG		CSA + PRED				CSA	PRED	AZA
	Number	Percent	Number	Percent	Number	Percent			
CSA Only	1	0.6	3	3.1	4	1.5	6.3	-	-
PRED Only	-	-	-	-	-	-	-	-	-
CSA + PRED	77	46.7	66	68.0	143	54.6	6.8	.24	-
CSA + AZA	-	-	1	1.0	1	0.4	4.4	-	0.4
AZA + PRED	6	3.6	-	-	6	2.3	-	.35	1.2
CSA + AZA + PRED	81	49.1	27	27.8	108	41.2	4.6	.24	1.0

Table 5-11
Immunosuppressive Protocol Nine Months Posttransplant, Overall and by Initial Immunosuppressive Protocol

	Initial Immunosuppressive Protocol				All Patients		Mean Drug Dosage (Mg/Kg/Day)		
	AZA + PRED + ALG		CSA + PRED				CSA	PRED	AZA
	Number	Percent	Number	Percent	Number	Percent			
CSA Only	-	-	1	1.6	1	0.7	3.8	-	-
PRED Only	-	-	-	-	-	-	-	-	-
CSA + PRED	46	51.7	41	65.1	87	57.2	6.2	.23	-
CSA + AZA	-	-	1	1.6	1	0.7	3.5	-	0.4
AZA + PRED	5	5.6	1	1.6	6	3.9	-	.30	1.1
CSA + AZA + PRED	38	42.7	19	30.2	57	37.5	4.0	.20	0.9

Table 5-12
Immunosuppressive Protocol 12 Months Posttransplant, Overall and by Initial Immunosuppressive Protocol

	Initial Immunosuppressive Protocol				All Patients		Mean Drug Dosage (Mg/Kg/Day)		
	AZA + PRED + ALG		CSA + PRED				CSA	PRED	AZA
	Number	Percent	Number	Percent	Number	Percent			
CSA Only	-	-	-	-	-	-	-	-	-
PRED Only	-	-	-	-	-	-	-	-	-
CSA + PRED	28	50.9	18	56.3	46	52.9	4.9	.22	-
CSA + AZA	1	1.8	1	3.1	2	2.3	3.0	-	0.8
AZA + PRED	6	10.9	-	-	6	6.9	-	.30	1.0
CSA + AZA + PRED	20	36.4	13	40.6	33	37.9	3.5	.19	0.9

(65.0%) or CSA + AZA + PRED (29.4%). However, of the patients who initially received CSA + PRED, 85.6 percent were on the same immunosuppressive protocol at the beginning of the three-month follow-up period. Approximately 10 percent of this group had been converted to CSA + AZA + PRED. Of the patients who initially received AZA + PRED + ALG, 54.5 percent were on CSA + PRED and 39.0 percent were on CSA + AZA + PRED at the beginning of the three-month follow-up period.

As shown in Table 5-9, three months following surgery the percentage of patients who were receiving CSA + PRED had decreased to 58.2 percent and the percentage of patients who were receiving CSA + AZA + PRED had increased to 36.6 percent. This was true for patients in both of the two initial immunosuppressive protocol groups. Among patients who initially received AZA + PRED + ALG, the percentage of patients receiving CSA + PRED had decreased to 50.2 percent and the percentage of patients receiving CSA + AZA + PRED had increased to 45.6 percent. Among patients who initially received CSA + PRED, the change was even greater. Three months following surgery, the percentage of patients receiving CSA + PRED had decreased to 74.8 percent and the percentage of patients receiving CSA + AZA + PRED had increased to 18.3 percent.

The same pattern was observed during the next three-month follow-up period. Six months posttransplant, the percentage of all patients in the study receiving CSA + PRED had decreased to 54.6 percent and the percentage of patients receiving CSA + AZA + PRED had increased to 41.2 percent. Again, the increase was observed for both initial immunosuppressive protocol groups, although the AZA + PRED + ALG group continued to have more patients on CSA + AZA + PRED than the CSA + PRED group. As can be seen in Table 5-10, 49.1 percent of patients who initially received AZA + PRED + ALG and 27.8 percent of patients who initially received CSA + PRED were receiving CSA + AZA + PRED six months following transplantation.

Immunosuppressive protocols at 9 and 12 months posttransplant show considerably less change, compared with immunosuppressive protocols six months posttransplant (Tables 5-11 and 5-12). One year posttransplant slightly over one-half of the patients in our study (52.9%) were receiving CSA + PRED, while 37.9 percent were receiving CSA + AZA + PRED.

In Table 5-13, we examine immunosuppressive drug protocol conversions in a slightly different manner. The table summarizes the drug conversions of individuals patients in the two predominant maintenance protocols--CSA + PRED and CSA + AZA + PRED--during each of the five follow-up data collection periods. As the table indicates, 241 patients were receiving CSA + PRED at the beginning of the three-month follow-up data collection period. Of these CSA + PRED patients, 17 patients died or experienced a graft failure during the first follow-up period. During this same period, 24 patients were converted from CSA + PRED to CSA + AZA + PRED and four patients were converted from CSA + PRED to another immunosuppressive protocol. In addition, seven patients were converted from other immunosuppressive protocols to CSA + PRED during the follow-up period. Thus, at the end of the first follow-up period, 203 patients were reported to be receiving CSA + PRED.

Similarly, 109 patients were receiving CSA + AZA + PRED at the beginning of the three-month follow-up data collection period. Of these CSA + AZA + PRED patients, four died or experienced a graft failure during the first follow-up period. Six CSA + AZA + PRED patients were converted to

Table 5-13
Immunosuppressive Drug Protocol Conversions of CSA + PRED and CSA + AZA + PRED Patients Following Transplant Surgery

	Discharge to 3 Months Posttransplant	3-6 Months Posttransplant	6-9 Months Posttransplant	9-12 Months Posttransplant	12-15 Months Posttransplant
Patients on CSA + PRED at Beginning of Follow-up Period	241	205	143	87	46
- Deaths and graft failures during period	-17	-4	-2	0	-2
- Conversions to CSA+AZA+PRED during period	-24	-22	-9	-8	-2
- Conversions to other protocols during period	-4	-1	0	0	0
+ Conversions to CSA+PRED during period	+7	+3	+1	+1	+2
Patients on CSA + PRED at End of Follow-up Period	203	181	133	80	44
Patients on CSA + AZA + PRED at Beginning of Follow-up Period	109	129	108	57	33
- Deaths and graft failures during period	-4	-6	-2	-1	0
- Conversions to CSA+PRED during period	-6	-3	-1	-1	-2
- Conversions to other protocols during period	-2	-1	-3	-3	0
+ Conversions to CSA+AZA+PRED during period	+29	+25	+9	+8	+2
Patients on CSA + AZA + PRED at End of Follow-up Period	126	144	111	60	33

CSA + PRED and two were converted to other immunosuppressive protocols. However, during this same period, a total of 29 patients were converted from other immunosuppressive protocols to CSA + AZA + PRED. Thus, during this first follow-up period, the number of patients who were receiving CSA + AZA + PRED increased from 109 to 126.

Table 5-13 also presents information on conversions for the periods 3-6 months posttransplant, 6-9 months posttransplant, 9-12 months posttransplant, and 12-15 months posttransplant. During each of the follow-up periods, the number of patients receiving CSA + PRED is greater at the beginning of the follow-up period than at the end of the period. Moreover, despite the loss of some patients to death and graft failure, the number of patients receiving CSA + AZA + PRED increased during each of the follow-up periods.

Clearly, the conversion of patients from CSA + PRED to CSA + AZA + PRED was most common during the first six months following transplantation. Between 6 and 12 months posttransplant, conversions from CSA + PRED to CSA + AZA + PRED occurred, but somewhat less frequently. Between 12 and 15 months posttransplant, very few patients were converted from one immunosuppressive drug protocol to another. In summary, these data suggest that, for the transplant centers included in our study, most conversions in transplant patients' immunosuppressive drug protocol occur within the first six months following surgery.

In addition to providing information on the numbers and percentages of patients on various immunosuppressive drug protocols following transplantation, Tables 5-8 through 5-12 also present information on the mean daily dosages of cyclosporine, prednisone and azathioprine. As shown in Table 5-8, patients on CSA + PRED received an average of 12.2 Mg/Kg/Day of cyclosporine and .52 Mg/Kg/Day of prednisone at the beginning of the three-month follow-up period (i.e., at discharge from the hospital following surgery). Patients on CSA + AZA + PRED received an average of 7.7 Mg/Kg/Day of cyclosporine, .51 Mg/Kg/Day of prednisone, and 1.0 Mg/Kg/Day of azathioprine. By six months posttransplant, patients on CSA + PRED received an average of 6.8 Mg/Kg/Day of cyclosporine and .24 Mg/Kg/Day of prednisone (see Table 5-10). By 12 months posttransplant, average doses had further decreased to 4.9 Mg/Kg/Day of cyclosporine and .22 Mg/Kg/Day of prednisone (see Table 5-12). Similar decreases were observed in the mean daily dosages of cyclosporine and prednisone among patients on CSA + AZA + PRED. Six months posttransplant, patients on CSA + AZA + PRED received an average of 4.6 Mg/Kg/Day of cyclosporine, .24 Mg/Kg/Day of prednisone, and 1.0 Mg/Kg/Day of azathioprine. By 12 months posttransplant, average doses were 3.5 Mg/Kg/Day of cyclosporine, .19 Mg/Kg/Day of prednisone, and 0.9 Mg/Kg/Day of azathioprine. Over time, average dosages of cyclosporine were decreased for both CSA + PRED and CSA + AZA + PRED patients. However, CSA + AZA + PRED patients consistently receive lower doses of cyclosporine than CSA + PRED patients.

Discussion

Tracking the experience of transplant recipients with immunosuppressive drugs is clearly an onerous task. Patients are frequently switched from one protocol to another. This implies a change in the drugs they receive. Moreover, the use of cyclosporine has further complicated the management of the transplant recipient. Some transplant teams rely on pharmacological monitoring to carefully prescribe drug dosages. Other teams adopt conventions based upon practice as to what are the appropriate dosages of drugs. Both approaches can lead to widely varying reports as to what are the appropriate dosages of all immunosuppressive agents. Moreover, when comparing published reports with established practice, there is frequently little consistency in the target dosages of drugs prescribed. For example, Table 5-14 compares drug dosages reported in the literature by the transplant centers participating in this study. In addition, the table shows the actual experience of these same transplant teams in this study. Clearly, in actual practice, at 12 months posttransplant, the dose of cyclosporine used by the double drug teams is half of what they report in the literature. The triple drug group is similar in principle and practice if the lower range of the cyclosporine dosage is accepted as the targeted dosage.

The inconsistency in the dosage of drugs administered makes it difficult to project the economic implications of various approaches to transplant immunosuppressive therapy. For example, does one assume the upper or lower level of targeted dosages? Chapter 13 is a detailed analysis of immunosuppressive drug costs for initial therapy and maintenance treatment based on both in-hospital and outpatient status. As will become evident, there are considerable differences in annual immunosuppressive drug costs based on the protocol followed. However, in light of the experience reported here, and summarized in Table 5-14, the estimates included in Chapter 13 may be viewed as too high, given the current practices of transplant teams throughout the United States. The trend is to use lower doses of cyclosporine in combination with other agents, thereby reducing total immunosuppressive drug expenditures per patient.

Table 5-14

Maintenance Immunosuppressive Drug Dosages Based on Published Reports and Actual Practice

	Initial Immunosuppressive Protocol Group	
Maintenance Protocol by Source	CSA + PRED	AZA + PRED + ALG
Published Reports		
CSA	10.0 mg/kg/day	4-8 mg/kg/day
PRED	.15-.22 mg/kg/day	.15-.22 mg/kg/day
AZA		1.0 mg/kg/day
Actual Experience		
CSA	4.9 mg/kg/day	3.5 mg/kg/day
PRED	.22 mg/kg/day	.19 mg/kg/day
AZA	-0-	0.9 mg/kg/day

CHAPTER 6

GRAFT AND PATIENT SURVIVAL

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CHAPTER 6 GRAFT AND PATIENT SURVIVAL

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Introduction

Patient and graft survival continue to be the primary criteria upon which the success of kidney transplantation is judged. Chapter 3 presented a detailed review of the survival results associated with a wide variety of transplant immunosuppressive protocols. Many of these entailed comparisons between conventional immunosuppressive therapy and some variation of cyclosporine therapy. Cyclosporine has definitely had a very positive impact on graft survival and relatively little effect on patient survival.

In a retrospective examination of survival rates even prior to the cyclosporine era, it is apparent that there was a relatively steady improvement in both graft and patient survival rates. Lowrie and colleagues (1973:863), for example, reported that among patients receiving transplants from cadaveric donors, graft survival rates increased from 40 to 50 percent during the period 1966 and 1977. Similarly, during this same period, cadaveric patient survival rates increased from 76 to 80 percent. Following the period, however, both patient and graft survival rates began to level off and occasionally took a turn for the worse. Marked improvement in graft survival rates among the recipients of cadaveric kidneys did not occur until cyclosporine was widely adopted in the United States but, as already indicated, cyclosporine had, for the most part, an insignificant effect on patient survival. At the time, however, patient survival rates were relatively high and, except in a very large series of patients, it was doubtful that a statistically significant association between cyclosporine and patient survival could be demonstrated.

Cyclosporine (either alone or in combination with other immunosuppressive drugs) increased one-year graft survival rates to 80 percent or better, compared with 50 to 60 percent for conventional protocols (e.g. prednisone and azathioprine). Thus, in very short order, based on the results of early clinical trials, cyclosporine was widely accepted as a superior immunosuppressive agent when compared with conventional immunosuppressive therapy. In more recent studies, many conducted following approval of cyclosporine by the United States Food and Drug Administration (FDA), cyclosporine has been shown to be particularly effective when used in combination with other immunosuppressive drugs.

In this chapter we examine both patient and graft survival of renal transplant patients in this study using a multivariate proportional hazards model. In our analysis, we investigate the effect of initial immunosuppressive protocol, and, in addition, we evaluate the influence that various transplant patient and donor characteristics have on survival. Our discussion is divided into three sections. In the first section we discuss the data and methods used in our analysis. In the second section we present actuarial estimates of patient and graft survival, overall as well as by initial immunosuppressive protocol. In the final section we present the results of our analysis of the factors influencing patient and graft survival among participating renal transplant recipients.

Data and Methods

In order to compute transplant patient and graft survival rates, the following information was required: date of transplantation, date of graft failure, and date of death. Each transplant program was asked to provide an update of the status of all patients who were eligible for the study as of

July 1, 1987.[1] The following information was obtained:

- Patient status as of July 1, 1987 (e.g., patient was still living with a functioning graft, patient experienced a graft failure and was retransplanted or returned to dialysis, patient died).
- Date of graft failure (for those patients who had experienced a graft failure).
- Date of death (for those patients who had died).

These data were collected for all patients who were determined to be eligible for the study. This included the 396 patients who initially agreed to participate in the study, as well as patients who for one of several reasons did not participate (e.g., they died before permission could be obtained, they experienced a graft failure before permission could be obtained, they were excluded for medical or social reasons, or they refused to participate in the study). It is likely that the patient and graft survival rates of the transplant patients who were eligible for the study, but were excluded for the above reasons, differ from the patient and graft survival rates of those transplant patients who agreed to participate in the study. Therefore, we felt that it was important to include these patients, to the extent possible, in our survival analysis.

Patient survival was measured from date of transplantation until date of death with right censoring for the end of the observation period (July 1, 1987). Graft survival was measured from date of transplantation until date of graft failure with right censoring for the end of the observation period (or the date of death if the patient died with a functioning graft). It should be noted that there are two commonly used methods of calculating graft survival. In the first method, the method we use in our analysis, patients are right censored if they die with a functioning graft. In the second method, rather than right censoring patients who die with a functioning graft, deaths are included as graft failures. From an epidemiological perspective, this second method may be a more meaningful measure of success; however, surgeons prefer the first method because they are not interested in failures unrelated to the technical success of the graft.

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[1] Time since transplant surgery varied between 8 and 20 months, depending upon when the particular patient's transplant surgery was performed.

Two separate analyses were performed. First, the SAS LIFETEST procedure was used to estimate survival rates of all patients eligible for inclusion in the study, as well as for patients grouped by initial immunosuppressive protocol. For the purpose of these analyses, patients were grouped according to the initial immunosuppressive drug protocol of the center at which their surgery was performed. The two initial immunosuppressive drug protocol groups are: patients who received cyclosporine and prednisone (CSA + PRED) and patients who received azathioprine, prednisone and antilymphocyte globulin (AZA + PRED + ALG). The AZA + PRED + ALG group consists of patients who received transplants at the following three centers: University of California, San Francisco; Ohio State University; and University of Wisconsin. The CSA + PRED group consists of patients who received transplants at the University of Pittsburgh and the University of Texas, Houston.

The SAS LIFEREG procedure was then used to determine the importance of initial immunosuppressive protocol, transplant recipient characteristics, and donor characteristics on graft and patient survival. More specifically, the following variables were included in the LIFEREG analysis:

- Initial immunosuppressive protocol.
- Age of recipient at time of transplant.

- Recipient race (e.g., white, black, other).
- Recipient sex.
- Primary renal diagnosis (e.g., diabetes, nondiabetes).
- Age of donor at time of death.
- Donor race (e.g., white, black).
- Donor sex.

The transplant recipient and donor characteristics listed above were obtained only for those 396 patients who agreed to participate in the study. Therefore, our analysis of the factors influencing graft and patient survival was restricted to this group of transplant patients.

Estimated Graft and Patient Survival

Early clinical trials in North America, Europe and Australia compared transplant patient and graft survival rates of patients receiving cyclosporine with those of patients receiving conventional immunosuppressive therapy (i.e., prednisone and azathioprine). In general, these studies reported improved graft survival for patients receiving cyclosporine (cyclosporine protocols produced one-year graft survival rates of 80 percent or better, compared with survival rates of 50 to 60 percent for conventional protocols). The impact of cyclosporine on patient survival, however, has been less significant.

Since cyclosporine has been widely accepted by most as a clearly superior immunosuppressive agent, transplant programs no longer utilize what was once regarded as conventional immunosuppressive therapy, instead administering cyclosporine in combination with a variety of other immunosuppressive agents. While many transplant programs administer cyclosporine and prednisone, some transplant programs (primarily in Europe) continue to use cyclosporine monotherapy. Evaluation of the effects of cyclosporine on graft and patient survival is further complicated because, in more recent years, triple and quadruple protocols have begun to emerge.

Thus, while it has been clearly demonstrated that higher graft survival rates are associated with protocols including cyclosporine (when compared with azathioprine and prednisone alone), studies have only begun to focus on differences in patient and graft survival rates of the various cyclosporine protocols in use today. In one very recent study, Ferguson (1988:285) compared a "sequential" immunosuppressive protocol (where ALG, azathioprine and prednisone are given for days 1 though 5 posttransplant, followed by low-dose cyclosporine and prednisone maintenance therapy) with a protocol of immediate cyclosporine without sequential therapy. Among patients who received a primary graft, those patients who received sequential therapy with delayed cyclosporine had a significantly better two-year graft survival rate (84%) compared with patients who received immediate cyclosporine therapy (74%).

In our analysis we compared graft survival rates of two initial immunosuppressive protocol groups--patients who initially received azathioprine, prednisone, and ALG and patients who initially received cyclosporine and prednisone--with similar results. Table 6-1 presents actuarial graft and patient survival rates of all eligible transplant recipients, overall and separately for the two initial immunosuppressive protocol groups, at 6 and 12 months posttransplant. At six months posttransplant, 84.9 percent of all eligible transplant patients still had functioning grafts. The one-year graft survival rate of all eligible transplant recipients was 82.4 percent. However, there was a tremendous difference in graft survival rates

Table 6-1

Actuarial Graft and Patient Survival Rates of All Eligible Transplant Recipients at 6 Months and 12 Months Posttransplant, Overall and by Initial Immunosuppressive Protocol

	All Patients	Initial Immunosuppressive Protocol AZA + PRED + ALG	CSA + PRED
Graft Survival (%)			
6 Months	84.9	90.7	75.7
12 Months	82.4	89.2	71.6
Patient Survival (%)			
6 Months	95.6	96.2	91.4
12 Months	94.3	95.2	89.8

by initial immunosuppressive protocol. Among those patients who initially received AZA + PRED + ALG, 90.7 percent still had functioning grafts six months following transplant surgery, compared with 75.7 percent of those patients who initially received CSA + PRED. One-year graft survival rates for the AZA + PRED + ALG group and the CSA + PRED group were 89.2 percent and 71.6 percent, respectively. Most graft failures occurred during the first six months following transplantation. Differences in the graft survival rates of the two initial immunosuppressive protocol groups during the first 180 days posttransplant are shown in Figure 6-1.

As shown in Table 6-1, 95.6 percent of all eligible transplant recipients, were living six months following their transplant surgery. The one-year patient survival rate of all eligible patients was 94.3 percent. Again, the two initial immunosuppressive protocol groups varied in terms of patient survival. Six months posttransplant, 96.2 percent of patients who initially received AZA + PRED + ALG were alive, compared with 91.4 percent of patients who initially received CSA + PRED. The one-year patient survival rate for the AZA + PRED + ALG patient group was 95.2 percent and for the CSA + PRED group the one-year patient survival rate was 89.9 percent. As was true in the case of graft failures, most patient deaths occurred in the first six months following transplant surgery. Figure 6-2 shows the patient survival rates of the two initial immunosuppressive protocol groups during the first 180 days posttransplant.

Factors Influencing Graft and Patient Survival

A number of previous studies have attempted to identify the factors influencing patient and graft survival of renal transplant patients. In one

Figure 6-1: Graft Survival by Initial Immunosuppressive Protocol

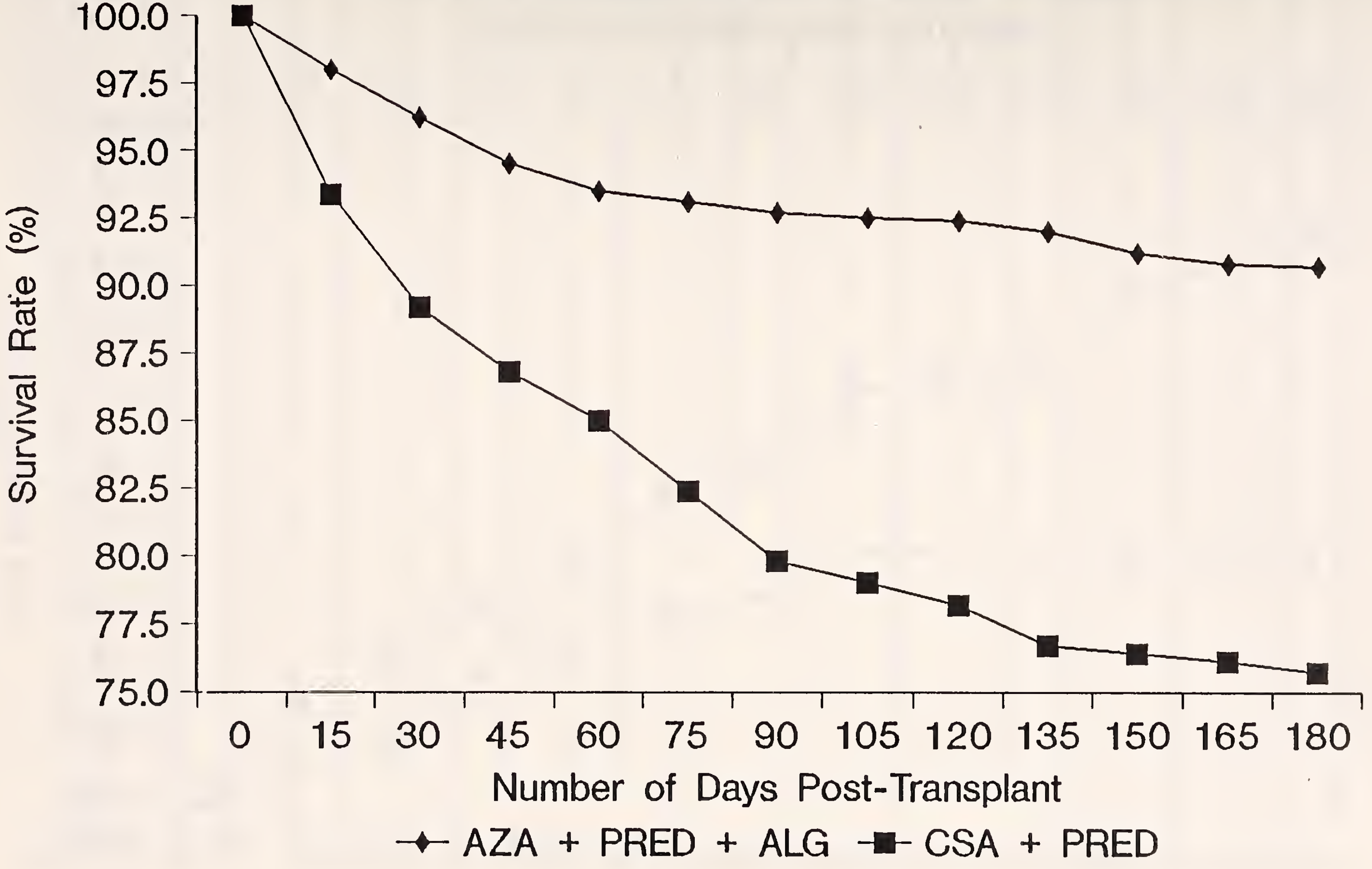
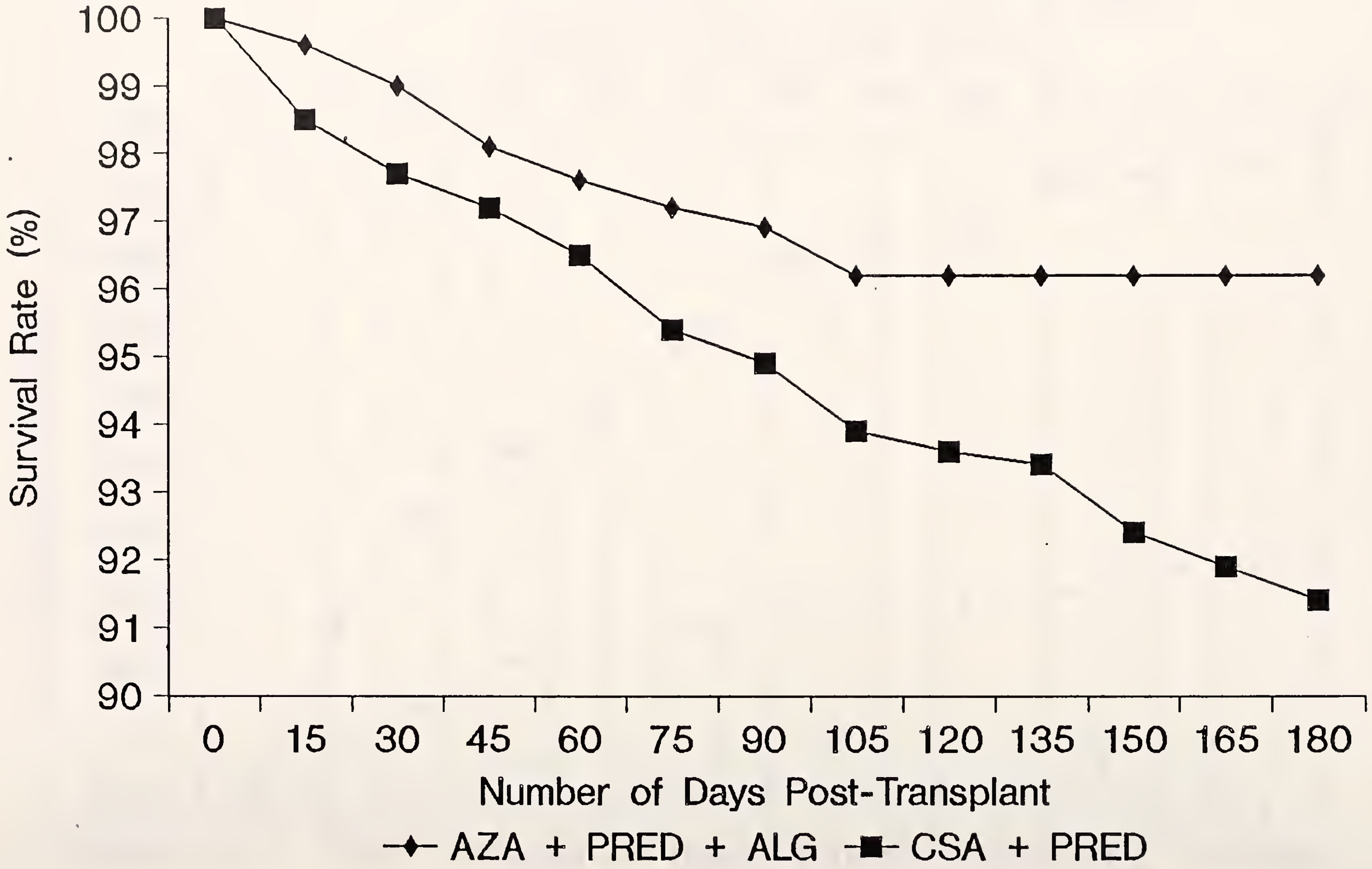


Figure 6-2: Patient Survival by Initial Immunosuppressive Protocol



such study, the Health Care Financing Administration examined transplant patient and graft survival of Medicare beneficiaries whose transplants occurred on or after January 1, 1982 through December 31, 1985. Among transplant recipients who received cadaveric grafts, 1-, 2-, and 3-year patient survival rates were 90.6 percent, 85.9 percent, and 81.1 percent, respectively. Patient survival decreased with advancing age, with three-year survival rates of 89 percent for persons less than 25 years old, falling to 68 percent for persons ages 65-74. Females had three-year survival rates about two percent greater than males (82.7% and 80.2% respectively). White persons, black persons, and Asian persons all had three-year survival rates of about 82 percent. Patient survival was lower among American Indians at 77.9 percent. Persons whose renal failure was attributed to glomerulonephritis had the highest three-year survival rate at 86.7 percent and persons with diabetes had the lowest three-year survival rate at 68.7 percent.

In terms of graft survival, among cadaver donor recipients, approximately two-thirds of the kidney grafts were functioning one year posttransplant and at three years just over one-half (52.1%) were still functioning.[2] There was little difference in graft survival across age and sex groups with almost all groups having three-year survival rates of about 50 percent. Asian and white transplant recipients had three-year graft survival rates of 55.8 percent and 54.3 percent, respectively. Lower graft survival rates were experienced by black recipients (44.6%) and American Indian recipients (41.3%). There were small differences in graft survival by primary disease category with persons with glomerulonephritis (54.3%) and polycystic kidney disease (56.8%) having higher survival rates than persons with hypertension (49.1%) and diabetes (48.9%).

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[2] It should be noted that in calculating these survival rates, patients who died with functioning grafts were not right censored. Thus, deaths were included as graft failures.

However, it should be recognized that most patients in the above study received their transplants before cyclosporine was approved by the Food and Drug Administration. More recent studies suggest that the use of cyclosporine has improved graft survival for a number of patient groups. For example, in a study of transplant patients from six transplant centers, Ferguson (1988:285) reported that there was no difference in one-year, two-year, and three-year graft survival rates among older and younger patients (i.e., those less than 50 years of age compared with those older than 50 years of age) receiving their first renal transplant. In this study, when a number of variables (e.g., degree of HLA, A, B, and DR match, total HLA match, age, pre-transplant transfusion and immunosuppressive protocol) were included in a Cox regression equation, only immunosuppressive protocol was significant in predicting graft survival. Those patients who received sequential therapy with delayed cyclosporine had a significantly better two-year graft survival rate compared with patients who received immediate cyclosporine therapy.

In our analysis of transplant patient and graft survival, information obtained from the Baseline Medical Records Data Abstraction Form (e.g., various transplant patient and donor characteristics) was available for each of the 396 patients who initially agreed to participate in the study. These variables were included in a proportional hazards model to identify possible factors influencing transplant patient and graft survival rates in the first 180 days posttransplant. We restricted our analysis to survival rates during the first 180 days following transplant surgery because most graft failures and deaths occurred in the first six months posttransplant (that is, few graft failures or deaths occurred between 8 and 20 months posttransplant). If included in the proportional hazards model, these outliers would have a disproportionate influence upon the model. This could potentially obscure the importance of the factors influencing graft and patient survival in the months immediately following transplant surgery. Thus, for the purposes of this analysis, patient survival was measured from date of transplantation until date of death with right censoring at six months posttransplant. Similarly, graft survival was measured from date of transplantation until date of graft failure with right censoring at six months posttransplant (or the date of death, if the patient died with a functioning graft).

In addition to initial immunosuppressive protocol, a number of transplant patient and donor characteristics were included as covariates in the patient and graft survival analyses. The following transplant patient characteristics were included: age at time of transplant, race, sex, and primary renal diagnosis (whether or not diabetes was the cause of renal failure). The following donor characteristics were included: age at time of death, race, and sex.

Surprisingly, neither transplant patient characteristics nor donor characteristics had a significant effect upon graft survival in the first 180 days following transplant surgery. The only variable that we were able to identify as a factor influencing graft survival was initial immunosuppressive protocol ($p < .001$). Those patients who initially received CSA + PRED had significantly lower graft survival rates in the first six months posttransplant compared with patients who initially received AZA + PRED + ALG. These results are consistent with the findings reported by Ferguson (1988:285) that patients who received sequential therapy with delayed cyclosporine had significantly better graft survival rates than patients who received immediate cyclosporine therapy.

The same transplant patient characteristics and donor characteristics were included as covariates in our analysis of patient survival in the first 180 days following transplant surgery. As was true for graft survival, the most important variable influencing patient survival was initial immunosuppressive protocol ($p < .07$). It should, however, be noted that initial immunosuppressive protocol had a much less significant impact on patient survival than it had on graft survival. Again, neither transplant patient characteristics nor donor characteristics had a significant effect upon patient survival.

Discussion

The results presented here suggest that initial immunosuppressive protocol is the single most important variable determining both graft and patient survival rates. In multivariate Cox proportional hazards models, all other transplant recipients and donor characteristics were found to be insignificant determinants of survival.

However, as noted in Chapter 2, three of the five participating transplant centers used an induction protocol of AZA + PRED + ALG exclusively, while the remaining two transplant centers used an induction protocol of CSA + PRED exclusively. Thus, in grouping centers according to their initial immunosuppressive drug protocol, it is not possible to distinguish the effects of immunosuppressive protocol from other characteristics of the transplant centers that could also influence graft and patient survival.

Our results are consistent with other studies that have focused on variations of cyclosporine immunosuppressive protocols. These studies have concluded that the superior protocol consists of azathioprine, prednisone, and ALG for induction, followed by the sequential introduction of cyclosporine as ALG therapy is discontinued. Maintenance therapy then consists of cyclosporine and prednisone or a combination of cyclosporine, prednisone, and azathioprine.

The results presented here emphasize the need to carefully document the various immunosuppressive protocols to which patients are exposed during the conduct of survival as well as other outcome analyses. Moreover, it is essential to distinguish between induction and maintenance protocols, as each of these have relevance in various outcome analyses. For example, multiple drug induction protocols are often criticized on grounds that infectious disease episodes are more frequent due to overimmunosuppression. The only way to take this into account is to have precise documentation of all the protocols to which each patient has been exposed. Finally, the results of this research definitely indicate that induction protocols have lasting effects that extend beyond the early posttransplant period.

CHAPTER 7

POSTTRANSPLANT CLINICAL COURSE OF KIDNEY TRANSPLANT RECIPIENTS

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Introduction

There is little disagreement that for the majority of patients with end-stage renal disease (ESRD), renal transplantation is superior to dialysis for long-term treatment. Studies have consistently shown that patients with functioning transplants have a quality of life that is vastly superior to that of patients on any form of dialysis (Belzer et al., 1983:99; Evans et al., 1985:553; Evans and Manninen, 1985:1579; Guttmann, 1979:975; Hart and Evans, 1987:117s; Johnson et al., 1982:286; Kutner, 1985:1579; Mathew et al., 1983:820; Parfrey et al., 1988:1231; Simmons et al., 1988:481; 1988:415; 1984:253; 1985:1577; Wood, 1983.).

Unfortunately, transplant recipients may suffer from a variety of both long- and short-term complications, as alluded to previously. Perhaps the most significant complication is graft failure. Kidney transplantation is the optimal form of therapy for ESRD only if it is successful. Troublesome is the fact that several studies have indicated that patients whose grafts fail often return to dialysis sicker than they were prior to transplantation (Johnson et al., 1982:286; Evans et al, 1987). Moreover, some patients remain sicker than they were prior to transplant for a considerable period of time. In this regard, transplantation represents a considerable risk to the stable dialysis patient.

Some of the complications transplant recipients experience are related to their transplant surgery, while others are a consequence of their need for maintenance immunosuppression. These complications have been reviewed at length by Crosnier (1981:232) and Tilney and Lazarus (1982:184). Surgical complications include the following: delayed healing and disruption of the incision, hemorrhage and perirenal abscess, urinary collection, development of lymphocele, vascular problems such as arterial stenosis, and urinary tract disorders that include reflux, stenosis, urinary fistulas and ureteral obstructions (Lacombe, 1975:283; Tilney, 1982:184; Tilney and Lazarus, 1982:98; Pfefferman et al., 1976:242; Schiff et al, 1976:251; Caralps et al., 1977:544). Infectious complications are also common among transplant recipients (Rubin et al., 1981:405; Tolkoff-Rubin and Rubin, 1988:554).

Bone and joint disorders are significant problems for transplant recipients (Crosnier, 1981:232; Murray, 1973:57; Woods et al., 1972:394; Ibels et al., 1978:25; Gottleib et al., 1982:125; Kenzora and Tilney, 1982:147). These are most often related to the administration of steroids. Arterial hypertension is among the more significant of the cardiovascular problems transplant recipients face (Crosnier, 1981:232; Tilney and Lazarus, 1982:98). Hematologic problems may occur with patients failing to achieve a normal hematocrit or secondarily developing anemia, even though renal function may be normal (Roman et al., 1972:1283). Transplant recipients may also develop leukopenia and thrombocytopenia, as well as polycythemia. Malignant tumors continue to be a source of concern (Penn, 1978:492; 1979:1047; 1982:71; 1983:2790; 1983:1079; 1984:492; 1987:32; 1987:276; 1988:439; Birkeland, 1983:1071; Kinlen et al., 1983:1039). Penn (1988:439) notes that data obtained by the Cincinnati Transplant Tumor Registry from several large transplant centers show a tumor incidence ranging from 1.0 to 16.0 percent of patients, with an average of 4.0 percent.

Other complications associated with organ transplantation include gastrointestinal disorders such as peptic ulcer, perforation and/or gastrointestinal hemorrhage (Crosnier et al., 1979:1361; Tilney et al., 1982:113); steroid diabetes resulting from chronic steroid administration; psychiatric disorders (Crosnier, 1981:232) and pancreatitis (Woods et al., 1972:193; Tilney et al., 1966:1051; Karrer et al., 1982:325; Johnson and Nabseth, 1970:309). Ophthalmic complications including cataract are fairly common, once again due to the administration of high dose steroids (Crosnier, 1981:232; Burns, 1982:170).

Finally, as described in Chapter 3, there are various side-effects associated with cyclosporine. These include: nephrotoxicity, hepatotoxicity, hirsutism, tremors, central nervous system toxicity, including seizures, gingival hyperplasia, hypertension, hemolytic anemia, thrombocytopenia, lymphoma, and lymphoproliferative disease (see Canadian Multicentre Transplant Study Group 1983:809; Merion et al., 1984:148).

Variables

In this chapter we examine various clinical outcomes of patients following transplant surgery. These outcomes include:

- Serum creatinine levels during each follow-up data collection period.
- Number of episodes of renal dysfunction.
- Adverse reactions to cyclosporine therapy.
- Frequency of symptoms and health-related problems.
- Comorbid conditions prior to and following transplantation.
- Number of times hospitalized during each follow-up data collection period.
- Number of disability days during each follow-up data collection period.

Much of the data presented in this chapter (i.e. renal function, adverse reactions to cyclosporine, other posttransplant complications) were obtained from the various Follow-up Medical Records Information Forms. These forms were completed by a data collector at the transplant center at three-month intervals following transplant surgery. In addition, information regarding symptoms and health-related problems, as well as hospitalizations and disability days following transplantation, were obtained from the Baseline and Follow-up Patient Questionnaires.

Results

Patient outcomes are examined at several points in time following transplantation--at 3-months, 6-months, 9-months, 12-months, and 15-months posttransplant. Clinical outcomes are examined separately for patients in the two initial immunosuppressive protocol groups (AZA + PRED + ALG versus CSA + PRED), as well as for patients grouped by primary renal diagnosis (diabetes versus nondiabetes). It should be recognized that since the follow-up period for patients in this study was 15 months or less, many of the long-term side-effects of the transplant patients' immunosuppressive therapy (for example, lymphomas) may not yet be apparent.

Our discussion of results is divided into four sections. The first section focuses on renal function following transplantation. In the second section we examine reported adverse reactions to cyclosporine. In the third section we examine other posttransplant complications--comparing comorbidity and the frequency of various symptoms and conditions following transplant surgery with the frequency of the same conditions prior to transplantation. The final section presents information concerning hospitalizations and disability days in the months following transplant surgery.

Renal Function Following Transplantation

Serum Creatinine Levels--

The Follow-up Medical Records Forms were used to collect information regarding transplant patients' renal function at three-month intervals in the months following surgery. Serum creatinine levels were used as one indication of renal function. The following three measures of serum creatinine were obtained for each follow-up period: the highest creatinine level measured during the period, the lowest creatinine level measured during the period, and the most recent creatinine level measured. Mean serum creatinine levels during the period from hospital discharge to three months posttransplant are shown in Table 7-1. The table presents the highest creatinine, lowest creatinine, and most recent creatinine for patients grouped by initial immunosuppressive protocol and primary renal diagnosis. In addition, the table compares the creatinine levels of patients who experienced a graft failure or died during the follow-up period with patients whose grafts were functioning at the end of the period.

For all patients included in the study, the mean highest creatinine measured during the period between initial hospital discharge and three months posttransplant was 3.3 mg/dl, while the mean lowest creatinine measured during this period was 1.7 mg/dl. The most recent creatinine level recorded was, on average, 2.3 mg/dl. Moreover, as can be seen in Table 7-1, renal function following transplantation varied by initial immunosuppressive protocol. Clearly, during the first three months posttransplant, patients who initially received AZA + PRED + ALG had better renal function than patients who initially received CSA + PRED. The most recent creatinine measured during the follow-up period was 2.1 mg/dl for AZA + PRED + ALG patients,

Table 7-1
Mean Serum Creatinine Levels During the Period From Hospital Discharge to Three Months Posttransplant by Initial Immunosuppressive Protocol, Primary Renal Diagnosis and Status During the Follow-up Period
(Standard deviation in parentheses)

	Highest Creatinine	Lowest Creatinine	Most Recent Creatinine
All Patients	3.3 (2.6)	1.7 (1.0)	2.3 (1.9)
Initial Immunosuppressive Protocol			
AZA + PRED + ALG	2.9 (2.2)	1.4 (0.5)	2.1 (1.7)
CSA + PRED	4.1 (3.0)	2.2 (1.5)	2.7 (2.1)
Primary Renal Diagnosis			
Nondiabetes	3.3 (2.6)	1.7 (1.1)	2.3 (1.9)
Diabetes	3.5 (2.5)	1.5 (0.5)	2.3 (1.8)
Status During the Follow-up Period			
Functioning graft	2.9 (1.7)	1.6 (0.6)	2.0 (1.0)
Graft failure or death during period	9.8 (4.9)	3.4 (3.0)	8.8 (4.1)

compared with 2.7 mg/dl for CSA + PRED patients. The superior renal function of the AZA + PRED + ALG initial immunosuppressive protocol group is also reflected in the highest and lowest creatinine levels measured during this period. Creatinine levels, however, did not vary by primary renal diagnosis.

Not surprisingly, the highest creatinine levels were recorded for those patients who died or experienced a graft failure during the follow-up period. For the 22 patients who died or had a graft failure during this period of time, the highest and lowest creatinine levels measured were, on average, 9.8 mg/dl and 3.4 mg/dl, respectively. These levels are considerably higher than the creatinine levels for those patients whose grafts were functioning at the end of the follow-up period.

Having examined differences in serum creatinine levels during the first three months posttransplant, we next studied creatinine levels during the remainder of the follow-up period. The highest serum creatinine levels measured during the initial follow-up period, as well as the highest serum creatinine levels measured during each subsequent three-month follow-up period, are shown in Table 7-2. Information is shown separately for patients grouped by initial immunosuppressive protocol, primary renal diagnosis and by status during the particular follow-up data collection period. Similar information regarding the lowest creatinine level measured during the period and the most recent creatinine level during each follow-up period are summarized in Tables 7-3 and 7-4.

Both the lowest serum creatinine levels measured (Table 7-3) and the most recent creatinine levels measured (Table 7-4) are relatively stable in the months following transplant surgery. The highest serum creatinine levels

Table 7-2
Highest Serum Creatinine During Patient Follow-up by Initial Immunosuppressive Protocol, Primary Renal Diagnosis and Status During the Follow-up Period (Standard deviation in parentheses)

	Mean Highest Creatinine Level During Period				
	Discharge to 3 Months Posttransplant	3-6 Months Posttransplant	6-9 Months Posttransplant	9-12 Months Posttransplant	12-15 Months Posttransplant
All Patients	3.3 (2.6)	2.7 (1.9)	2.4 (1.3)	2.4 (1.7)	2.6 (1.8)
Initial Immunosuppressive Protocol					
AZA + PRED + ALG	2.9 (2.2)	2.4 (1.8)	2.2 (1.1)	2.1 (0.9)	2.3 (1.3)
CSA + PRED	4.1 (3.0)	3.2 (2.0)	2.7 (1.6)	2.9 (2.4)	3.1 (2.4)
Primary Renal Diagnosis					
Nondiabetes	3.3 (2.6)	2.7 (1.9)	2.3 (1.1)	2.5 (1.9)	2.6 (2.0)
Diabetes	3.5 (2.5)	2.7 (1.9)	2.6 (1.8)	2.3 (0.9)	2.5 (1.1)
Status During Follow-up Period					
Functioning graft	2.9 (1.7)	2.4 (1.2)	2.2 (0.9)	2.3 (1.0)	2.5 (1.7)
Graft failure or death during period	9.8 (4.9)	9.3 (4.2)	9.7 (2.1)	19.8 (-)	5.7 (3.3)

Table 7-3
Lowest Serum Creatinine During Patient Follow-up by Initial Immunosuppressive Protocol, Primary Renal Diagnosis and Status During the Follow-up Period
(Standard deviation in parentheses)

	Mean Lowest Creatinine Level During Period				
	Discharge to 3 Months Posttransplant	3-6 Months Posttransplant	6-9 Months Posttransplant	9-12 Months Posttransplant	12-15 Months Posttransplant
All Patients	1.7 (1.0)	1.7 (0.8)	1.7 (0.7)	1.7 (0.6)	1.8 (0.6)
Initial Immunosuppressive Protocol					
AZA + PRED + ALG	1.4 (0.5)	1.5 (0.7)	1.6 (0.5)	1.6 (0.5)	1.6 (0.6)
CSA + PRED	2.2 (1.5)	2.0 (0.8)	2.0 (0.9)	2.0 (0.7)	2.0 (0.6)
Primary Renal Diagnosis					
Nondiabetes	1.7 (1.1)	1.7 (0.8)	1.7 (0.7)	1.7 (0.7)	1.7 (0.6)
Diabetes	1.5 (0.5)	1.6 (0.7)	1.7 (0.9)	1.7 (0.6)	1.8 (0.7)
Status During Follow-up Period					
Functioning graft	1.6 (0.6)	1.6 (0.5)	1.7 (0.6)	1.7 (0.6)	1.7 (0.6)
Graft failure or death during period	3.4 (3.0)	3.7 (2.2)	4.6 (2.1)	4.6 (-)	2.3 (1.4)

Table 7-4
Most Recent Serum Creatinine During Patient Follow-up by Initial Immunosuppressive Protocol, Primary Renal Diagnosis and Status During the Follow-up Period
(Standard deviation in parentheses)

	Mean Recent Creatinine Level During Period				
	Discharge to 3 Months Posttransplant	3-6 Months Posttransplant	6-9 Months Posttransplant	9-12 Months Posttransplant	12-15 Months Posttransplant
All Patients	2.3 (1.9)	2.1 (1.5)	2.0 (1.1)	2.0 (1.3)	2.1 (1.1)
Initial Immunosuppressive Protocol					
AZA + PRED + ALG	2.1 (1.7)	2.0 (1.6)	1.8 (0.9)	1.7 (0.7)	2.0 (1.3)
CSA + PRED	2.7 (2.1)	2.3 (1.1)	2.3 (1.3)	2.5 (1.7)	2.3 (0.8)
Primary Renal Diagnosis					
Nondiabetes	2.3 (1.9)	2.0 (1.5)	1.9 (1.0)	2.1 (1.4)	2.1 (1.1)
Diabetes	2.3 (1.8)	2.2 (1.5)	2.1 (1.3)	1.9 (0.7)	2.2 (1.1)
Status During Follow-up Period					
Functioning graft	2.0 (1.0)	1.9 (0.8)	1.9 (0.7)	1.9 (0.8)	2.0 (0.8)
Graft failure or death during period	8.8 (4.1)	8.1 (5.4)	7.3 (4.1)	13.6 (-)	5.5 (3.1)

reported, as shown in Table 7-2, decrease during the three to six month follow-up period when compared with the period from discharge to three months posttransplant. Following this initial decline in the highest creatinine levels reported, the highest creatinine levels remained quite stable over the remainder of the follow-up data collection period. (As will be seen later, the initial reduction in the highest creatinine levels reported reflects a decrease in the frequency of episodes of renal dysfunction experienced over time.) Moreover, it is noteworthy that patients who initially receive AZA + PRED + ALG continue to have better renal function throughout the follow-up period than patients who initially receive CSA + PRED.

Episodes of Renal Dysfunction--

As another measure of renal function following transplant surgery, information concerning the number of episodes of renal dysfunction experienced during each follow-up data collection period were obtained from the patients' medical records. Information on the number of episodes of renal dysfunction during the period from discharge from the hospital following transplant surgery to three months posttransplant is summarized in Table 7-5. The table provides information for all patients, as well as for patients grouped by initial immunosuppressive protocol and primary renal diagnosis. Of all patients included in the study, 50.8 percent had one or more episodes of renal dysfunction during the period from hospital discharge to three months posttransplant. As shown in Table 7-5, the mean number of episodes of renal dysfunction during this period was .95. Of the 351 episodes of renal dysfunction that were reported during this period, 47.3 percent were

Table 7-5
Episodes of Renal Dysfunction During the Period From Hospital Discharge to Three Months Posttransplant by Initial Immunosuppressive Protocol and Primary Renal Diagnosis

	All Patients	Primary Renal Diagnosis		Initial Immunosuppressive Protocol	
		Nondiabetes	Diabetes	AZA + PRED + ALG	CSA + PRED
Total number of patients	370	271	99	246	124
Patients with one or more episodes of renal dysfunction (%)	50.8	50.2	52.5	43.9	64.5
Number of episodes of renal dysfunction per patient ($\bar{X}$)	.95	.96	.92	.84	1.17
Total number of episodes of renal dysfunction	351	260	91	206	145
Episodes of renal dysfunction diagnosed as nephrotoxicity (%)	47.3	47.3	47.3	43.2	53.1
Episodes of renal dysfunction requiring hospitalization (%)	45.0	43.1	50.5	49.0	39.3

diagnosed as nephrotoxicity. Almost one-half (45.0%) of these episodes of renal dysfunction required hospitalization.

As can be seen in Table 7-5, the number of episodes of renal dysfunction varied for the two initial immunosuppressive protocol groups. Patients who initially received CSA + PRED experienced more episodes of renal dysfunction than patients who initially received AZA + PRED + ALG and, furthermore, these episodes of renal dysfunction were more likely to be diagnosed as nephrotoxicity. For example, during the period from hospital discharge to three months posttransplant, 64.5 percent of the patients who initially received CSA + PRED experienced one or more episodes of renal dysfunction, compared with only 43.9 percent of the patients who initially received AZA + PRED + ALG. During this time period CSA + PRED patients averaged 1.17 episodes of renal dysfunction, while AZA + PRED + ALG patients averaged .84. It is noteworthy, however, that although CSA + PRED patients experienced more renal dysfunction, fewer of the episodes of renal dysfunction required hospitalization.

As can be seen in Table 7-5, the number of episodes of renal dysfunction reported during the first three months posttransplant did not differ by primary renal diagnosis. However, in the case of diabetic patients, a somewhat higher percentage of the episodes of renal dysfunction required hospitalization.

Next, we examined the number of episodes of renal dysfunction experienced by participating transplant recipients with increasing time since transplantation. As shown in Table 7-6, the frequency of episodes of renal dysfunction experienced by transplant patients decreased over time. During the period between hospital discharge and three months posttransplant 50.8

Table 7-6
Episodes of Renal Dysfunction Following Transplant Surgery

	Time Period				
	Discharge to 3 Months Posttransplant	3-6 Months Posttransplant	6-9 Months Posttransplant	9-12 Months Posttransplant	12-15 Months Posttransplant
Total number of patients	370	352	261	151	87
Patients with one or more episodes of renal dysfunction (%)	50.8	29.8	17.6	14.6	10.2
Number of episodes of renal dysfunction per patient ($\overline{X}$)	.95	.45	.24	.28	.21
Total number of episodes of renal dysfunction	351	159	62	42	18
Episodes of renal dysfunction diagnosed as nephrotoxicity (%)	47.3	52.2	62.9	54.8	50.0
Episodes of renal dysfunction requiring hospitalization (%)	45.0	35.8	29.0	47.6	50.0

percent of patients experienced one or more episodes of renal dysfunction, compared with only 10.2 percent of patients during the period from 12-15 months posttransplant. This decrease is also reflected in the mean number of episodes of renal dysfunction--the number of episodes per patient decreased from .95 during the period from hospital discharge to three months posttransplant to .45 during the period from 3-6 months posttransplant. The average further decreased to .24 episodes per patient during the period from 6-9 months posttransplant and remained relatively stable during the remainder of the follow-up data collection period.

Tables 7-7 and 7-8 present information regarding episodes of renal dysfunction following transplant surgery by initial immunosuppressive protocol and primary renal diagnosis, respectively. The number of episodes of renal dysfunction experienced by transplant patients decreased over time for both nondiabetic and diabetic patients, as well as for both initial immunosuppressive protocol groups. The decline is particularly dramatic in the case of the CSA + PRED patient group, perhaps due to the tapering of cyclosporine. As shown in Table 7-7, by 6-9 months posttransplant, the frequency of episodes of renal dysfunction among patients who initially received CSA + PRED was no higher than that for patients who initially received AZA + PRED + ALG. It is important to mention that the numbers presented in Tables 7-7 and 7-8 appear rather unstable for the later time periods (e.g., beyond nine months posttransplant). This is related to the fact that, because not all patients were included in the study for the entire 15 month follow-up data collection period, the number of patients in the various patient subgroups is relatively small for the later time periods. Because of the small number of patients in these subgroups, and the decreasing number

Table 7-7
Episodes of Renal Dysfunction Following Transplant Surgery by Initial Immunosuppressive Protocol

	Time Period									
	Discharge to 3 Months Posttransplant		3-6 Months Posttransplant		6-9 Months Posttransplant		9-12 Months Posttransplant		12-15 Months Posttransplant	
	AZA+PRED+ALG	CSA+PRED	AZA+PRED+ALG	CSA+PRED	AZA+PRED+ALG	CSA+PRED	AZA+PRED+ALG	CSA+PRED	AZA+PRED+ALG	CSA+PRED
Total number of patients	246	124	237	115	165	96	88	63	55	32
Patients with one or more episodes of renal dysfunction (%)	43.9	64.5	28.3	33.0	18.8	15.6	20.5	6.3	14.5	3.1
Number of episodes of renal dysfunction per patient ($\bar{X}$)	.84	1.17	.39	.57	.25	.21	.32	.22	.27	.09
Total number of episodes of renal dysfunction	206	145	93	66	42	20	28	14	15	3
Episodes of renal dysfunction diagnosed as nephrotoxicity (%)	43.2	53.1	63.4	36.4	76.2	35.0	64.3	35.7	53.3	33.3
Episodes of renal dysfunction requiring hospitalization (%)	49.0	39.3	35.5	36.4	26.2	35.0	35.7	71.4	46.7	66.7

Table 7-8
Episodes of Renal Dysfunction Following Transplant Surgery by Primary Renal Diagnosis

	Time Period									
	Discharge to 3 Months Posttransplant		3-6 Months Posttransplant		6-9 Months Posttransplant		9-12 Months Posttransplant		12-15 Months Posttransplant	
	Nondiabetes	Diabetes	Nondiabetes	Diabetes	Nondiabetes	Diabetes	Nondiabetes	Diabetes	Nondiabetes	Diabetes
Total number of patients	271	99	258	94	193	68	115	36	63	24
Patients with one or more episodes of renal dysfunction (%)	50.2	52.5	30.2	28.7	18.1	16.2	13.9	16.7	7.9	16.7
Number of episodes of renal dysfunction per patient ($\bar{X}$)	.96	.92	.46	.44	.24	.24	.26	.33	.08	.46
Total number of episodes of renal dysfunction	260	91	118	41	46	16	30	12	7	11
Episodes of renal dysfunction diagnosed as nephrotoxicity (%)	47.3	47.3	55.1	43.9	67.4	50.0	53.3	58.3	42.9	54.5
Episodes of renal dysfunction requiring hospitalization (%)	43.1	50.5	29.7	53.7	13.0	56.3	53.3	33.3	71.4	36.4

of episodes of renal dysfunction during these later follow-up periods, the percentages shown for these later time periods appear unstable.

Adverse Reactions to Cyclosporine

Information concerning adverse reactions to cyclosporine was obtained from patients' medical records at three-month intervals following transplantation. The adverse reactions experienced by patients during the period from initial discharge from the hospital following surgery to three months posttransplant are presented in Table 7-9. The information is provided for all patients, as well as for patients grouped by primary renal diagnosis and initial immunosuppressive protocol. Of those patients who received cyclosporine during the follow-up period, the two most commonly reported adverse reactions were tremors (49.0%) and hypertension (43.5%). Other adverse reactions experienced by patients during this period include muscle weakness (22.4%), hirsutism (17.2%), hyperkalemia (14.1%), paresthesias (10.5%), temperature sensitivity (6.6%), gingival hyperplasia (5.5%) and hyperuricemia (5.0%). The other reactions shown in Table 7-9 were experienced by less than two percent of the patients who received cyclosporine.

As can be seen in Table 7-9, diabetic and nondiabetic patients were equally likely to experience most adverse reactions to cyclosporine. However, it should be noted that the percentages of patients who experienced tremors and hypertension were higher among nondiabetic patients. With respect to initial immunosuppressive protocol, more interesting differences emerge. Clearly, the extent to which patients experience adverse reactions to cyclosporine during the first three months posttransplant varied depending

Table 7-9
Adverse Reactions to Cyclosporine During the Period Between Hospital Discharge and Three Months Posttransplant by Initial Immunosuppressive Protocol and Primary Renal Diagnosis*

	All Patients	Primary Renal Diagnosis		Initial Immunosuppressive Protocol	
		Nondiabetes	Diabetes	AZA+PRED+ALG	CSA+PRED
Tremors (%)	49.0	52.7	39.2	39.9	66.7
Paresthesias (%)	10.5	9.5	13.4	5.0	21.1
Muscle Weakness (%)	22.4	23.1	20.6	16.8	33.3
Temperature Sensitivity (%)	6.6	7.6	4.1	7.1	5.7
Seizures (%)	1.1	1.5	0.0	0.8	1.6
Hepatic Toxicity (%)	1.9	1.9	2.1	0.4	4.9
Hirsutism (%)	17.2	17.4	16.5	5.9	39.0
Lymphoma (%)	0.6	0.4	1.0	0.8	0.0
Hyperuricemia (%)	5.0	5.7	3.1	4.2	6.5
Hyperkalemia (%)	14.1	13.6	15.5	15.1	12.2
Hypertension (%)	43.5	48.5	29.9	34.5	61.0
Gingival Hyperplasia (%)	5.5	6.4	3.1	1.3	13.8

*Patients experiencing various adverse reactions expressed as a percentage of all patients receiving cyclosporine during the period.

upon when the patients' cyclosporine therapy was begun. Patients who initially received CSA + PRED experienced more adverse reactions to cyclosporine within the first three months posttransplant compared with patients who initially received AZA + PRED + ALG. As shown in Table 7-9, the two most commonly reported adverse reactions to cyclosporine--tremors and hypertension--were reported more often for patients who initially received CSA + PRED. Patients who initially received CSA + PRED were also more like to experience paresthesias, muscle weakness, hirsutism, and gingival hyperplasia during the first three months posttransplant than were patients who initially received AZA + PRED + ALG. For example, gingival hyperplasia was a problem for 13.8 percent of CSA + PRED patients during the first three months posttransplant, while only 1.3 percent of AZA + PRED + ALG patients experienced this problem. Finally, although only 1.9 percent of all patients in the study experienced hepatic toxicity in the three months following transplantation, 4.9 percent of patients who initially received CSA + PRED suffered from hepatic toxicity compared with only 0.4 percent among patients who initially received AZA + PRED + ALG. These findings are not particularly surprising since, as we observed in Chapter 5, patients who initially received CSA + PRED received higher dosages of cyclosporine than patients who initially received AZA + PRED + ALG.

Having examined the adverse reactions to cyclosporine experienced by patients during the first three months posttransplant, we next examined the extent to which these adverse reactions to cyclosporine continue with increasing time since transplantation. As shown in Table 7-10, as dosages of cyclosporine are reduced, most of the negative side-effects associated with cyclosporine therapy decrease with increasing time since transplantation.

Table 7-10
Adverse Reactions to Cyclosporine During Patient Followup*

	Discharge to 3 Months Posttransplant	3-6 Months Posttransplant	6-9 Months Posttransplant	9-12 Months Posttransplant	12-15 Months Posttransplant
Tremors (%)	49.0	23.9	15.1	12.2	10.3
Paresthesias (%)	10.5	6.6	5.4	4.8	2.3
Muscle Weakness (%)	22.4	12.9	6.9	2.7	2.3
Temperature Sensitivity (%)	6.6	2.0	0.8	0.0	0.0
Seizures (%)	1.1	1.1	0.0	0.7	1.1
Hepatic Toxicity (%)	1.9	1.4	0.4	0.0	0.0
Hirsutism (%)	17.2	15.5	8.9	4.1	2.3
Lymphoma (%)	0.6	0.0	0.0	0.0	0.0
Hyperuricemia (%)	5.0	10.3	8.9	12.2	4.6
Hyperkalemia (%)	14.1	7.5	2.3	4.1	2.3
Hypertension (%)	43.5	44.5	47.1	47.6	43.7
Gingival Hyperplasia (%)	5.5	4.0	4.6	2.7	2.3

*Patients experiencing various adverse reactions expressed as a percentage of all patients receiving cyclosporine during the period.

Tremors, which were experienced by 49.0 percent of all patients during the period from discharge to three months posttransplant, were experienced by only 10.3 percent of the patients during the period from 12 to 15 months posttransplant. Similarly, muscle weakness had been a problem for 22.4 percent of all transplant patients between discharge and three months posttransplant, compared with only 2.3 percent of patients during the period from 12 to 15 months posttransplant. Also, fewer patients experienced paresthesias, temperature sensitivity, hirsutism, hyperkalemia, and gingival hyperplasia with increasing time since transplantation. The one major side-effect of cyclosporine therapy that did not show an improvement over time is hypertension. As can be seen in Table 7-10, the percentage of patients with hypertension remained relatively constant over time.

Tables 7-11 and 7-12 present comparisons of the adverse reactions experienced by transplant patients at three month intervals during the period from discharge to 15 months posttransplant by initial immunosuppressive protocol and primary renal diagnosis, respectively. Both diabetic and nondiabetic patients, as well as patients in both initial immunosuppressive protocol groups, experienced fewer negative side-effects of their cyclosporine therapy with increasing time since transplantation. Furthermore, it is interesting to note that the large difference between the two immunosuppressive protocol groups in terms of the problems observed in the first three months posttransplant is greatly reduced over time. As can be seen in Table 7-11, the adverse reactions experienced by the two groups 12 to 15 months posttransplant do not differ greatly. Hypertension, however, is the one difference that appears to persist over time. Based on the information obtained from the patients medical records, CSA + PRED patients

Table 7-11
Adverse Reactions to Cyclosporine During Patient Followup by Initial Immunosuppressive Protocol*

	Discharge to 3 Months Posttransplant		3-6 Months Posttransplant		6-9 Months Posttransplant		9-12 Months Posttransplant		12-15 Months Posttransplant	
	AZA + PRED + ALG	CSA + PRED	AZA + PRED + ALG	CSA + PRED	AZA + PRED + ALG	CSA + PRED	AZA + PRED + ALG	CSA + PRED	AZA + PRED + ALG	CSA + PRED
Tremors (%)	39.9	66.7	16.7	38.3	16.0	13.4	14.3	9.5	12.7	6.3
Paresthesias (%)	5.0	21.1	5.2	9.6	5.6	5.2	1.2	9.5	1.8	3.1
Muscle Weakness (%)	16.8	33.3	11.2	16.5	5.6	9.3	2.4	3.2	0.0	6.3
Temperature Sensitivity (%)	7.1	5.7	1.7	2.6	0.0	2.1	0.0	0.0	0.0	0.0
Seizures (%)	0.8	1.6	0.9	1.7	0.0	0.0	1.2	0.0	1.8	0.0
Hepatic Toxicity (%)	0.4	4.9	0.4	3.5	0.6	0.0	0.0	0.0	0.0	0.0
Hirsutism (%)	5.9	39.0	5.6	35.7	4.3	16.5	1.2	7.9	1.8	3.1
Lymphomas (%)	0.8	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Hyperuricemia (%)	4.2	6.5	9.9	11.3	11.1	5.2	16.7	6.3	5.5	3.1
Hyperkalemia (%)	15.1	12.2	9.0	4.3	3.7	0.0	6.0	1.6	3.6	0.0
Hypertension (%)	34.5	61.0	42.9	47.8	43.2	53.6	42.9	54.0	30.9	65.6
Gingival Hyperplasia (%)	1.3	13.8	0.4	11.3	1.2	10.3	0.0	6.3	0.0	6.3

*Patients experiencing various adverse reactions expressed as a percentage of all patients receiving cyclosporine during the period.

Table 7-12
Adverse Reactions to Cyclosporine During Patient Followup by Primary Renal Diagnosis*

	Discharge to 3 Months Posttransplant		3-6 Months Posttransplant		6-9 Months Posttransplant		9-12 Months Posttransplant		12-15 Months Posttransplant	
	Non-Diabetes	Diabetes	Non-Diabetes	Diabetes	Non-Diabetes	Diabetes	Non-Diabetes	Diabetes	Non-Diabetes	Diabetes
Tremors (%)	52.7	39.2	25.9	18.3	16.7	10.4	14.2	5.9	9.5	12.5
Paresthesias (%)	9.5	13.4	4.7	11.8	4.2	9.0	5.3	2.9	1.6	4.2
Muscle Weakness (%)	23.1	20.6	10.2	20.4	6.8	7.5	1.8	5.9	3.2	0.0
Temperature Sensitivity (%)	7.6	4.1	2.0	2.2	1.0	0.0	0.0	0.0	0.0	0.0
Seizures (%)	1.5	0.0	0.8	2.2	0.0	0.0	0.9	0.0	1.6	0.0
Hepatic Toxicity (%)	1.9	2.1	1.7	1.1	0.0	1.5	0.0	0.0	0.0	0.0
Hirsutism (%)	17.4	16.5	15.7	15.1	8.9	9.0	3.5	5.9	1.6	4.2
Lymphomas (%)	0.4	1.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Hyperuricemia (%)	5.7	3.1	12.2	5.4	9.9	6.0	13.3	8.8	6.3	0.0
Hyperkalemia (%)	13.6	15.5	6.7	9.7	2.1	3.0	3.5	5.9	3.2	0.0
Hypertension (%)	48.5	29.9	49.4	31.2	51.6	34.3	46.0	52.9	46.0	37.5
Gingival Hyperplasia (%)	6.4	3.1	4.3	3.2	5.7	1.5	3.5	0.0	3.2	0.0

*Patients experiencing various adverse reactions expressed as a percentage of all patients receiving cyclosporine during the period.

consistently experience more hypertension than AZA + PRED + ALG patients in the months following transplantation.

Other Posttransplant Complications

Disease Symptomatology and Health-Related Problems--

Information concerning various posttransplant complications was obtained from the Baseline and Follow-up Patient Questionnaires. Patients were given a list of symptoms and health-related problems and asked to indicate how often (i.e., often, sometimes, rarely, or never) they experienced each of them just before they had their kidney transplant. They were then given the same list of problems and asked to indicate how often they have experienced each of them since they received their transplant. The percentages of patients reporting that they experienced these problems "often" are presented in Table 7-13.

As can be seen in Table 7-13, patients reported that they frequently experienced a rather large number of symptoms and health-related problems prior to receiving their transplant. Over two-thirds of all patients indicated that they often experienced tiring easily/no energy and weakness/lack of strength before receiving their kidney transplant. Likewise, over one-third said that they often experienced aches/swelling/ sick feeling; muscle weakness; high potassium; and high concentration of uric acid in their blood. Finally, over one-quarter of all patients reported that they often experienced nervousness/tension/anxiety and shortness of breath/trouble breathing prior to their kidney transplant.

As is obvious from Table 7-13, however, patients reported considerably fewer symptoms and health-related problems in the period following their

Table 7-13
Frequency of Symptoms and Health Related Problems Prior to and Three Months Following Transplant Surgery (Percent reporting that they experienced problems often)

	Before Transplant	3 Months Posttransplant
Pain	22.4	6.7
Tiring Easily, No Energy	77.9	13.0
Weakness, Lack of Strength	69.1	16.6
Aches, Swelling, Sick Feeling	41.9	5.9
Fainting Spells, Dizziness	16.2	2.8
Nervousness, Tension, Anxiety	25.5	9.5
Shortness of Breath, Trouble Breathing	26.1	4.7
Depression	23.2	6.7
Tremors	6.3	13.5
Muscle Weakness	37.6	15.8
Temperature Sensitivity	21.9	10.8
Seizures	1.5	0.4
Extra Body Hair Growth	5.9	55.3
High Potassium	37.6	4.4
High Concentration of Uric Acid in Blood	36.7	2.9

transplant surgery. With the exception of tremors and extra body hair growth--side-effects of their immunosuppressive therapy--patients reported lower levels of all listed conditions for the period since their transplant compared with the levels reported for the period just prior to their transplant surgery. For example, 77.9 percent of patients said that they often experienced tiring easily/no energy prior to their transplant, but only 13.0 percent responded similarly three months following their transplant surgery. Likewise, 69.1 percent of the patients said that they often experienced weakness/lack of strength prior to their surgery, compared with only 16.6 percent following their surgery.

Tables 7-14 and 7-15 present the frequency of these symptoms and health-related problems, by initial immunosuppressive protocol and primary renal diagnosis. For most conditions, the percentage of patients who said that they often experienced a particular symptom prior to receiving their transplant was somewhat higher among patients who initially received AZA + PRED + ALG than among patients who initially received CSA + PRED. More specifically, AZA + PRED + ALG patients were more likely than CSA + PRED to say that they often experienced symptoms such as pain; tiring easily/no energy; weakness/lack of strength; aches/swelling/sick feeling; shortness of breath/trouble breathing; muscle weakness; and high concentration of uric acid in the blood prior to transplantation. Three months posttransplant, however, the percentages of patients reporting that they often experienced these symptoms were more similar for the two groups. However, as noted earlier, the CSA + PRED patients, who received high doses of cyclosporine, were more likely than AZA + PRED + ALG patients to report adverse reactions to cyclosporine (e.g., nervousness/tension/anxiety; tremors;

Table 7-14
Frequency of Symptoms and Health Related Problems Prior to and Three Months Following Transplant Surgery by Initial Immunosuppressive Protocol
(Percent reporting that they experienced problems often)

	Before Transplant		3 Months Posttransplant	
	AZA+PRED+ALG	CSA+PRED	AZA+PRED+ALG	CSA+PRED
Pain	25.9	14.9	7.1	6.0
Tiring Easily, No Energy	83.8	65.5	12.4	14.5
Weakness, Lack of Strength	72.4	62.1	15.9	18.1
Aches, Swelling, Sick Feeling	44.9	35.6	5.3	7.2
Fainting Spells, Dizziness	16.8	14.9	3.5	1.2
Nervousness, Tension, Anxiety	24.9	26.7	6.5	15.7
Shortness of Breath, Trouble Breathing	30.3	17.2	3.5	7.2
Depression	24.3	20.7	6.5	7.2
Tremors	6.0	6.9	11.2	18.1
Muscle Weakness	43.5	25.3	15.3	16.9
Temperature Sensitivity	23.2	18.6	8.8	14.5
Seizures	2.2	0.0	0.6	0.0
Extra Body Hair Growth	6.0	5.8	51.8	62.7
High Potassium	38.1	36.5	3.6	9.8
High Concentration of Uric Acid in Blood	41.4	26.0	2.5	3.8

Table 7-15
Frequency of Symptoms and Health Related Problems Prior to and Three Months Following Transplant Surgery by Primary Renal Diagnosis
(Percent reporting that they experienced problems often)

	Before Transplant		3 Months Posttransplant	
	Nondiabetes	Diabetes	Nondiabetes	Diabetes
Pain	21.7	24.6	6.9	6.2
Tiring Easily, No Energy	74.4	88.4	13.3	12.3
Weakness, Lack of Strength	64.5	82.6	16.0	18.5
Aches, Swelling, Sick Feeling	36.5	58.0	6.9	3.1
Fainting Spells, Dizziness	16.7	14.5	1.6	6.2
Nervousness, Tension, Anxiety	22.8	33.3	10.1	7.7
Shortness of Breath, Trouble Breathing	28.6	18.8	4.8	4.6
Depression	19.7	33.3	6.9	6.2
Tremors	7.4	2.9	15.5	7.7
Muscle Weakness	36.1	42.0	15.4	16.9
Temperature Sensitivity	22.0	21.7	11.2	9.4
Seizures	2.0	0.0	5.3	0.0
Extra Body Hair Growth	7.5	1.4	57.4	49.2
High Potassium	38.9	33.8	4.3	4.7
High Concentration of Uric Acid in Blood	39.9	27.0	3.9	0.0

temperature sensitivity; and extra body hair growth).

With respect to primary renal diagnosis, diabetic patients were more likely than nondiabetic patients to say that they often experienced various symptoms and health-related problems prior to transplantation. As can be seen in Table 7-15, a higher percentage of diabetic patients reported that they often experienced tiring easily/no energy; weakness/lack of strength; aches/swelling/sick feeling; nervousness/ tension/anxiety; depression; and muscle weakness prior to transplantation. Three months posttransplant, however, there was little difference between the two groups with respect to the frequency of symptoms and health related-problems.

Finally, patients were asked similar questions regarding the frequency of these same symptoms and health-related conditions at 6-months, 9-months, 12-months, and 15-months posttransplant. As previously observed, many of the side-effects of cyclosporine therapy (e.g., tremors, muscle weakness, extra body hair growth) decrease somewhat with increasing time since transplantation. However, as shown in Table 7-16, the frequency with which most symptoms are reported remains relatively constant over time.

Comorbid Conditions--

Comorbidity among transplant patients at the time of their transplant surgery, based on information contained in the patient's medical records, was briefly examined in Chapter 4. In this chapter, we examine the presence of various comorbid conditions three months' following transplantation and compare this with comorbid conditions present prior to transplantation. In addition, we present information concerning comorbid conditions developed during the period from 3-15 months posttransplant.

Table 7-16
Frequency of Symptoms and Health Related Problems Prior to and Three Months Following Transplant Surgery
(Percent reporting that they experienced problems often)

	Before Transplant	3 Months Posttransplant	6 Months Posttransplant	9 Months Posttransplant	12 Months Posttransplant	15 Months Posttransplant
Pain	22.4	6.7	12.6	6.6	6.7	13.5
Tiring Easily, No Energy	77.9	13.0	18.3	19.2	13.5	17.3
Weakness, Lack of Strength	69.1	16.6	15.3	17.9	7.9	17.3
Aches, Swelling, Sick Feeling	41.9	5.9	7.8	5.3	6.7	7.7
Fainting Spells, Dizziness	16.2	2.8	2.6	1.3	1.1	0.0
Nervousness, Tension, Anxiety	25.5	9.5	7.4	8.6	10.1	11.5
Shortness of Breath, Trouble Breathing	26.1	4.7	3.1	7.2	4.5	5.9
Depression	23.2	6.7	4.8	6.6	5.7	11.5
Tremors	6.3	13.5	6.6	8.7	6.8	3.8
Muscle Weakness	37.6	15.8	10.5	12.6	8.0	3.9
Temperature Sensitivity	21.9	10.8	9.2	7.9	3.4	7.8
Seizures	1.5	0.4	0.4	0.7	0.0	0.0
Extra Body Hair Growth	5.9	55.3	55.7	40.8	42.0	32.7
High Potassium	37.6	4.4	5.2	4.1	5.7	3.9
High Concentration of Uric Acid in Blood	36.7	2.9	4.5	4.8	2.3	6.0

Information regarding comorbidity following transplantation was obtained from the Baseline and Follow-up Patient Questionnaires. For each condition listed, patients were asked to report whether they had the condition before transplantation, three-months posttransplant, both before transplantation and three-months posttransplant, or never. A summary of the responses to this series of questions is presented in Table 7-17.

In addition to their kidney disease, a fairly large percentage of transplant patients reported having hypertension (74.5%), vision disorders (53.7%), sleep disorders (42.4%), diabetes (26.1%) and nervous or emotional problems (25.6%) prior to their transplant. Not surprisingly, a high percentage of the patients reported having these same conditions three months posttransplant; however, the percentages reporting hypertension and sleep disorders were lower.

Table 7-18 compares the comorbid conditions reported by renal transplant patients prior to transplantation, as well as three months posttransplant, by initial immunosuppressive protocol. Table 7-19 presents a similar comparison for patients grouped by primary renal diagnosis. As can be seen in Table 7-18, there are few differences between the two initial immunosuppressive protocol groups with respect to pretransplant comorbidity or comorbidity three months following transplantation. Also, as shown in Table 7-19, with the exception of those comorbid conditions related to their diabetes (e.g., diabetes; missing finger, hand, arm, toe, foot, or leg; vision disorder), diabetic and nondiabetic patients reported similar levels of comorbidity for both time periods.

Finally, as part of each Follow-up Patient Questionnaire patients were asked whether or not they had developed any of the comorbid conditions

Table 7-17
Comorbid Conditions Experienced by Participating Transplant Recipients Prior to and Three Months Following Transplant Surgery

	Year Prior to Transplant	3 Months Posttransplant
Cancer (%)	2.2	0.4
Chronic Lung Disorder (%)	4.1	2.6
Stomach Ulcer (%)	17.7	6.6
Colitis, Gastritis (%)	12.5	8.5
Chronic Kidney Disorder (%)	88.4	9.0
Diabetes (%)	26.1	32.0
Hepatitis (%)	5.9	0.0
Other Liver Disorder (%)	3.0	1.8
Hypertension (%)	74.5	52.4
Hardening of Arteries or Arteriosclerosis (%)	5.2	4.8
Angina, Myocardial Infarction (%)	7.4	2.2
Epileptic Seizures or Convulsions (%)	4.8	1.5
Cerebrovascular Accident, including Stroke (%)	4.1	0.0
Bone Disease (%)	8.1	3.7
Back or Spine Disorder (%)	8.8	7.0
Paralysis (%)	2.2	1.5
Arthritis or Rheumatism (%)	18.8	18.5
Missing Finger, Hand, Arm, Toe, Foot, or Leg (%)	5.2	5.5
Vision (Sight) Disorder (%)	53.7	57.7
Hearing Disorder (%)	13.7	15.1
Nervous or Emotional Problems (%)	25.6	21.1
Mental Disorder (%)	1.5	1.5
Alcohol or Drug Problems (%)	3.3	1.5
Sleep Disorder (%)	42.4	23.6
Skin Disorder (%)	18.4	20.6
Migraine (%)	13.6	6.6
Gum Disorder (%)	7.7	8.5

Table 7-18
Comorbid Conditions Experienced by Participating Transplant Recipients Prior to and Three Months Following Transplant Surgery by Initial Immunosuppressive Protocol

	Year Prior to Transplant		3 Months Posttransplant	
	AZA+PRED+ALG	CSA+PRED	AZA+PRED+ALG	CSA+PRED
Cancer (%)	1.1	4.6	0.0	1.1
Chronic Lung Disorder (%)	4.9	2.3	1.6	4.6
Stomach Ulcer (%)	17.9	17.2	4.9	10.3
Colitis, Gastritis (%)	10.9	16.1	5.4	14.9
Chronic Kidney Disorder (%)	91.2	82.6	8.3	10.5
Diabetes (%)	26.5	25.3	31.9	32.2
Hepatitis (%)	5.5	6.9	0.0	0.0
Other Liver Disorder (%)	3.8	1.1	1.6	2.3
Hypertension (%)	73.9	75.9	51.1	55.2
Hardening of Arteries or Arteriosclerosis (%)	5.9	3.5	5.4	3.5
Angina, Myocardial Infarction (%)	8.7	4.6	2.7	1.1
Epileptic Seizures or Convulsions (%)	5.9	2.3	1.6	1.1
Cerebrovascular Accident, including Stroke (%)	5.4	1.1	0.0	0.0
Bone Disease (%)	9.7	4.6	4.3	2.3
Back or Spine Disorder (%)	9.7	6.9	6.5	8.0
Paralysis (%)	2.7	1.1	1.1	2.3
Arthritis or Rheumatism (%)	17.9	20.7	17.4	20.7
Missing Finger, Hand, Arm, Toe, Foot, or Leg (%)	4.9	5.7	5.4	5.7
Vision (Sight) Disorder (%)	54.6	51.7	57.3	58.6
Hearing Disorder (%)	17.4	5.7	16.8	11.5
Nervous or Emotional Problems (%)	30.1	16.1	19.7	24.1
Mental Disorder (%)	1.6	1.1	2.2	0.0
Alcohol or Drug Problems (%)	3.3	3.4	1.6	1.1
Sleep Disorder (%)	45.7	35.6	21.2	28.7
Skin Disorder (%)	20.0	14.9	21.1	19.5
Migraine (%)	14.6	11.5	6.5	6.9
Gum Disorder (%)	8.7	5.7	6.0	13.8

Table 7-19
Comorbid Conditions Experienced by Participating Transplant Recipients Prior to and Three Months Following Transplant Surgery by Primary Renal Diagnosis

	Year Prior to Transplant		3 Months Posttransplant	
	Nondiabetes	Diabetes	Nondiabetes	Diabetes
Cancer (%)	3.0	0.0	0.5	0.0
Chronic Lung Disorder (%)	4.5	2.9	3.0	1.4
Stomach Ulcer (%)	18.3	15.9	7.4	4.3
Colitis, Gastritis (%)	11.9	14.5	8.9	7.2
Chronic Kidney Disorder (%)	88.0	89.6	10.0	6.0
Diabetes (%)	3.0	94.2	9.4	98.6
Hepatitis (%)	5.9	5.9	0.0	0.0
Other Liver Disorder (%)	4.0	0.0	2.5	0.0
Hypertension (%)	71.8	82.6	52.0	53.6
Hardening of Arteries or Arteriosclerosis (%)	4.0	8.7	3.5	8.7
Angina, Myocardial Infarction (%)	6.9	8.8	1.5	4.4
Epileptic Seizures or Convulsions (%)	6.4	0.0	2.0	0.0
Cerebrovascular Accident, including Stroke (%)	3.5	5.8	0.0	0.0
Bone Disease (%)	8.4	7.2	3.0	5.8
Back or Spine Disorder (%)	9.9	5.8	7.4	5.8
Paralysis (%)	2.0	2.9	1.0	2.9
Arthritis or Rheumatism (%)	20.3	14.5	19.3	15.9
Missing Finger, Hand, Arm, Toe, Foot, or Leg (%)	2.5	13.0	2.0	15.9
Vision (Sight) Disorder (%)	40.9	91.3	48.3	85.5
Hearing Disorder (%)	15.3	8.7	16.3	11.6
Nervous or Emotional Problems (%)	24.8	27.9	19.3	26.5
Mental Disorder (%)	2.0	0.0	2.0	0.0
Alcohol or Drug Problems (%)	3.0	4.3	0.5	4.3
Sleep Disorder (%)	45.0	34.8	24.3	21.7
Skin Disorder (%)	20.2	13.0	20.2	21.7
Migraine (%)	14.8	10.1	8.9	0.0
Gum Disorder (%)	8.9	4.3	10.4	2.9

listed in Table 7-20 during the previous three months. The most commonly reported conditions developed during patient follow-up were hypertension, vision disorders, nervous or emotional problems, sleep disorders, skin disorders, and gum disorders. As discussed in the previous section, these problems are frequently side-effects of transplant recipients' immunosuppressive therapy.

Hospitalizations and Disability Days

In this section we examine hospitalizations and disability days in the months following transplant surgery. Information regarding hospitalizations during the follow-up data collection period were obtained from two sources--from the Medical Records maintained by the transplant center and from the patient as part of the Baseline and Patient Follow-up Questionnaires. It should be noted that the information from these two sources is likely to differ. There are several reasons to expect differences in the information from the two sources.

First, patient survey data were not obtained for all patients included in the study. This reflects the fact that not all patients initially agreed to participate in the patient portion of the study, and not all patients who initially agreed to participate returned completed questionnaires. Thus, the patients for whom hospitalization data are available are not the same for the two data sources. This problem is not serious, unless the hospital utilization of those transplant recipients who elected not to participate in the patient surveys differs from the hospitalization utilization of those transplant recipients who did participate. Unfortunately, given our study design, the two groups differ in one very important regard--in the inclusion of patients

Table 7-20
Conditions Developed by Participating Transplant Recipients Following Transplant Surgery

	3-6 Months Posttransplant	6-9 Months Posttransplant	9-12 Months Posttransplant	12-15 Months Posttransplant
Cancer (%)	0.0	0.0	0.0	0.0
Chronic Lung Disorder (%)	1.3	0.7	0.0	1.9
Stomach Ulcer (%)	0.4	1.3	0.0	1.9
Colitis, Gastritis (%)	2.6	2.6	1.1	1.9
Chronic Kidney Disorder (%)	1.3	2.0	1.1	0.0
Diabetes (%)	5.2	3.9	2.2	1.9
Hepatitis (%)	0.4	0.0	0.0	0.0
Other Liver Disorder (%)	0.9	0.7	0.0	0.0
Hypertension (%)	15.5	5.9	5.6	7.7
Hardening of Arteries or Arteriosclerosis (%)	0.4	0.7	0.0	0.0
Angina, Myocardial Infarction (%)	0.4	0.0	0.0	0.0
Epileptic Seizures or Convulsions (%)	0.0	0.0	0.0	0.0
Cerebrovascular Accident, including Stroke (%)	0.0	0.0	0.0	0.0
Bone Disease (%)	1.7	2.6	2.2	1.9
Back or Spine Disorder (%)	4.3	2.0	4.5	0.0
Paralysis (%)	0.0	0.0	0.0	0.0
Arthritis or Rheumatism (%)	5.2	7.2	3.4	7.7
Missing Finger, Hand, Arm, Toe, Foot, or Leg (%)	0.9	0.7	1.1	1.9
Vision (Sight) Disorder (%)	23.3	13.8	13.5	23.1
Hearing Disorder (%)	6.5	4.6	2.2	3.8
Nervous or Emotional Problems (%)	11.6	7.2	2.2	9.6
Mental Disorder (%)	0.9	0.7	0.0	0.0
Alcohol or Drug Problems (%)	0.0	0.0	0.0	0.0
Sleep Disorder (%)	12.5	7.2	11.2	5.8
Skin Disorder (%)	19.4	12.5	5.6	5.8
Migrane (%)	4.3	0.0	4.5	1.9
Gum Disorder (%)	10.8	7.9	7.9	15.4

who died or experienced a graft failure during the various follow-up data collection periods. If a patient experienced a graft failure or died during a particular follow-up period, one final Follow-up Medical Records Form was completed for the patient (to capture the hospital costs associated with the graft failure or death). However, if the patient died or experienced a graft failure, no additional Follow-up Patient Questionnaires were administered. Thus, the hospital utilization data obtained from transplant center medical records include information for patients who died or had graft failures during the follow-up period; whereas, the data provided by patients include information only for those patients who had functioning grafts at the end of the follow-up data collection period. Since those patients who experienced graft failures or who died during a particular period are more likely to have been hospitalized than patients with functioning grafts, the information provided by patients may slight underreport hospitalizations in the months following transplantation.

Second, although an attempt was made to obtain data for the same time periods, in some cases patients may not have provided data for the same time period for which the medical records information were reported. The hospitalizations obtained from patients' medical records were based on specific dates (for example, the exact three-month or six-month anniversary of the transplant). In contrast, for the hospitalization data obtained from patients, patients were asked about hospitalization in the last three months (or, in the case of the Baseline Patient Questionnaire, since discharge from the hospital following their transplant operation). If a patient completed the questionnaire on, or soon after, the 3, 6, 9, 12, or 15 month anniversary of their surgery, then the data collected from the two sources were for the same time period.

However, in some instances patients were late in completing questionnaires. In such cases the time periods reported may not have been identical.

Another reason for possible differences in the reported number of hospitalizations is related to the way in which the questions were asked. Patients were asked to report the number of times they were hospitalized overnight for any condition. The Follow-up Medical Records Form, on the other hand, requested information on all hospital discharges. Patients who were admitted and discharged on the same day (for example, for minor surgery) were therefore reported as a hospital stay by the data collector at the transplant center, but were not reported by the patient. Also, the Follow-up Medical Records Form specifically requested information regarding the number of times the patient was discharged from the hospital during the follow-up period. If a patient was hospitalized at the end of the follow-up period, the hospital stay was not reported until the next follow-up period (when the patient was discharged from the hospital). A patient, on the other hand, may have said that they were hospitalized during both of the follow-up periods. A fourth reason for a difference between the two sources may result from the fact that patients are more likely to report hospital stays in hospitals other than the transplant center. If stays outside the transplant center were not recorded on the patient's medical record, the hospital stay may not have been reported on the Follow-up Medical Records Form. In such cases the Medical Records would underreport the actual number of hospital stays during a particular follow-up period. A final factor explaining a possible difference between the two sources of information is, of course, the problem of patient recall.

Recognizing that there are potential problems the with accuracy of data from both sources, we chose to obtain data from both patients and from transplant center medical records. However, before examining hospitalizations in the months following transplant surgery, we begin this section with an examination of hospitalizations in the year prior to transplantation.

Hospitalizations in the Year Prior to Transplantation--

Patients were asked two questions regarding the number of times hospitalized, and the number of nights hospitalized in the year prior to receiving their transplant. Responses to these questions, overall as well as by initial immunosuppressive protocal and primary renal diagnosis, are summarized in Table 7-21. Over one-quarter of all patients (27.9%) reported that they were not hospitalized in the year prior to transplantation and another 31.2 percent had been hospitalized only one or two times. As can be seen in Table 7-21, however, a small percentage of patients reported that they were hospitalized several times during the year--13.2 percent of the patients indicated that they were hospitalized five or more times. The total number of nights spent in the hospital in the year prior to the transplant surgery ranged from 0 (for those who were not hospitalized) to a maximum of 120 nights. While most patients (40.8%) were hospitalized between 1 and 15 nights, nearly 10 percent of all patients reported that they spent more than 30 nights in the hospital in the year prior to their transplant surgery.

Hospitalizations in the year prior to transplantation did not differ by initial immunosuppressive protocol. However, as is clearly shown in Table 7-21, diabetic patients had much higher hospital utilization in the year prior to transplantation than did nondiabetic patients. Among nondiabetic patients, 34.5 percent said they were not hospitalized in the year prior to their

Table 7-21
Hospitalizations in the Year Prior to Transplant Surgery by Initial Immunosuppressive Protocol and Primary Renal Diagnosis

	All Patient	Primary Renal Diagnosis		Initial Immunosuppressive Protocol	
		Nondiabetes	Diabetes	AZA+PRED+ALG	CSA + PRED
Number of Times Hospitalized					
0 Times (%)	27.9	34.5	8.7	27.6	28.7
1 Time (%)	17.6	19.2	13.0	16.2	20.7
2 Times (%)	13.6	13.3	14.5	14.6	11.5
3 Times (%)	16.9	15.3	21.7	15.1	20.7
4 Times (%)	8.1	5.9	14.5	8.6	6.9
5 Times (%)	4.0	3.0	7.2	5.4	1.1
6 or More Times (%)	9.2	5.9	18.8	9.7	8.1
No Response/Don't Know (%)	2.6	3.0	1.4	2.7	2.3
Total Number of Nights Hospitalized					
0 Nights (%)	27.9	34.5	8.7	27.6	28.7
1-3 Nights (%)	9.6	10.8	5.8	8.6	11.5
4-6 Nights (%)	7.0	6.4	8.7	6.5	8.0
7-9 Nights (%)	9.9	10.8	7.2	9.2	11.5
10-15 Nights (%)	14.3	13.8	15.9	14.1	14.9
16-20 Nights (%)	7.8	6.4	11.6	9.7	3.4
21-25 Nights (%)	3.3	3.0	4.3	3.8	2.3
26-30 Nights (%)	4.4	2.5	10.1	4.3	4.6
31 or More Nights (%)	9.9	6.4	20.3	10.3	9.2
No Response/Don't Know (%)	5.9	5.4	7.2	5.9	5.7

surgery, compared with only 8.7 percent of diabetic patients. Similarly, 26.0 percent of diabetic patients reported that they were hospitalized five or more times, while the corresponding percentage for nondiabetic patients was 8.9 percent. The higher rate of hospital utilization of diabetic patients is also reflected in the number of nights hospitalized. In the year prior to transplant surgery, 20.3 percent of diabetic patients said that they spent 31 or more nights in the hospital compared with only 6.4 percent of nondiabetic patients.

Hospitalizations and Disability Days Following Transplant Surgery--

The Follow-up Medical Records Information Forms, which were completed by a transplant center staff member at 3, 6, 9, 12, and 15-months posttransplant, were used to obtain information regarding hospitalizations following transplant surgery. As described in Chapter 2, the first Follow-up Medical Records Information Form covered the period from hospital discharge following transplant surgery until three months posttransplant. All other follow-up periods were of a three-month duration, unless the patient died or experienced a graft failure during the follow-up period. The Follow-up Medical Records Information Form asked for the number of times that the patient was discharged from the hospital during the particular follow-up period,[1] and for each hospital discharge, the number of days hospitalized (information regarding the costs associated with each hospital stay were also requested and are presented in Chapter 12).

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[1] It should be recognized that if a person was hospitalized at the end of a particular follow-up period, the information was not reported until the next follow-up period--the period during which the patient was discharged from the hospital.

The number of hospital discharges during each follow-up period and the total number of days hospitalized during each follow-up period for patients grouped by initial immunosuppressive protocol are summarized in Table 7-22. Table 7-23 presents similar information for patients grouped by primary renal diagnosis. As can be seen in Table 7-22, hospital utilization during the first 15 months posttransplant does not vary by initial immunosuppressive protocol. Furthermore, hospital utilization for both groups decreases with increasing time since transplantation. During the period between initial hospital discharge and three months posttransplant, approximately one-half (49.7%) of the transplant recipients included in the study were hospitalized one or more times. Of those patients hospitalized, most were hospitalized only once and most were hospitalized for ten days or less. However, 11 percent of all patients were hospitalized two or more times during this period and slightly over five percent of all patients were hospitalized for a total of 26 or more days.

Beyond six months posttransplant, approximately 20 percent of all patients in the study were hospitalized during each three-month follow-up data collection period and, of those hospitalized, most were hospitalized for a total of ten days or less during the three-month period. Only 20.4 percent of all patients were hospitalized one or more times during the period between 9 and 12 months posttransplant. Similarly, only 24.1 percent of all patients had been hospitalized one or more times between 12 and 15 months posttransplant. This pattern of decreasing hospital utilization with the passage of time can be observed for patients regardless of initial immunosuppressive drug protocol.

Earlier we observed that diabetic patients were hospitalized more often than nondiabetic patients in the year prior to transplant surgery. As can be

Table 7-22
Number of Hospital Discharges and Number of Days Hospitalized Following Transplant Surgery by Initial Immunosuppressive Protocol

	Discharge to 3 Months Posttransplant		3-6 Months Posttransplant		6-9 Months Posttransplant		9-12 Months Posttransplant		12-15 Months Posttransplant	
	AZA+PRED+ALG	CSA+PRED	AZA+PRED+ALG	CSA+PRED	AZA+PRED+ALG	CSA+PRED	AZA+PRED+ALG	CSA+PRED	AZA+PRED+ALG	CSA+PRED
Number of Hospital Discharges										
0 Times (%)	51.2	48.4	73.6	67.8	82.4	79.4	79.8	79.4	72.7	81.3
1 Time (%)	38.2	37.9	22.1	24.3	13.9	15.5	14.6	12.7	23.6	12.5
2 Times (%)	7.3	7.3	3.8	7.0	3.6	3.1	4.5	6.3	3.6	6.3
3 Times (%)	2.4	6.5	0.4	0.9	0.0	2.1	1.1	1.6	0.0	0.0
4 Times (%)	0.4	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
5 Times (%)	0.4	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Number of Days Hospitalized										
0 Days (%)	51.2	48.4	73.6	67.8	82.4	79.4	79.8	79.4	72.7	81.3
1-3 Days (%)	11.0	7.3	7.2	3.5	2.4	3.1	5.6	6.3	9.1	3.1
4-6 Days (%)	11.0	8.1	3.4	5.2	4.3	2.1	3.4	1.6	3.6	3.1
7-10 Days (%)	6.5	9.7	5.5	7.8	4.9	6.2	3.4	4.8	5.5	9.4
11-15 Days (%)	6.1	9.7	4.7	4.3	1.8	5.2	2.2	0.0	1.8	0.0
16-20 Days (%)	6.5	5.6	2.1	5.2	0.6	1.0	1.1	3.2	1.8	0.0
21-25 Days (%)	2.8	4.8	1.7	0.9	0.6	0.0	0.0	1.6	0.0	0.0
26 or More Days (%)	4.5	6.5	1.3	5.2	2.4	3.1	3.4	3.2	3.6	3.1
Don't Know (%)	0.4	0.0	0.4	0.0	0.6	0.0	1.1	0.0	1.8	0.0

Table 7-23
Number of Hospital Discharges and Number of Days Hospitalized Following Transplant Surgery by Primary Renal Diagnosis

	Discharge to 3 Months Posttransplant		3-6 Months Posttransplant		6-9 Months Posttransplant		9-12 Months Posttransplant		12-15 Months Posttransplant	
	Nondiabetes	Diabetes	Nondiabetes	Diabetes	Nondiabetes	Diabetes	Nondiabetes	Diabetes	Nondiabetes	Diabetes
Number of Hospital Discharges										
0 Times (%)	53.5	41.4	73.8	66.0	86.1	67.6	84.3	64.9	81.0	62.5
1 Time (%)	34.7	47.5	21.5	26.6	11.9	22.1	10.4	24.3	15.9	29.2
2 Times (%)	7.4	7.1	4.3	6.4	1.5	8.8	5.2	5.4	3.2	8.3
3 Times (%)	4.1	3.0	0.4	1.0	0.5	1.5	0.0	5.4	0.0	0.0
4 Times (%)	0.0	1.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
5 Times (%)	0.4	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Number of Days Hospitalized										
0 Days (%)	53.5	41.4	73.8	66.0	86.1	67.6	84.3	64.9	81.0	62.5
1-3 Days (%)	8.1	14.1	6.3	5.3	2.1	4.4	7.0	2.7	6.3	8.3
4-6 Days (%)	9.2	12.1	4.7	2.1	3.1	4.4	0.9	8.1	1.6	8.3
7-10 Days (%)	7.4	8.1	5.9	7.4	5.2	5.9	1.7	10.8	4.8	12.5
11-15 Days (%)	8.1	5.1	2.3	10.6	2.1	5.9	0.9	2.7	1.6	0.0
16-20 Days (%)	5.2	9.1	2.7	4.3	0.5	1.5	1.7	2.7	0.0	4.2
21-25 Days (%)	3.0	5.1	1.6	1.1	0.0	1.5	0.9	0.0	0.0	0.0
26 or More Days (%)	5.5	4.0	2.3	3.2	1.0	7.4	2.6	5.4	4.8	0.0
Don't Know (%)	0.0	1.0	0.4	0.0	0.0	1.5	0.0	2.7	0.0	4.2

seen in Table 7-23, diabetic patients continue to be hospitalized more often than non diabetic patient in the months following transplantation. For example, during the period between hospital discharge and three months posttransplant, 58.6 percent of diabetic patients were hospitalized one or more times compared with 46.5 percent of nondiabetic patients. While hospital utilization for both diabetic and nondiabetic patients decreases over time during the first 15 months following transplant surgery, diabetic patients continue to be hospitalized more than nondiabetic patients.

In addition to obtaining information on subsequent hospitalizations from the patients' medical records, patients were asked to provide information concerning hospitalizations at three-month intervals during the months following transplantation as part of the Baseline and Follow-up Patient Questionnaires. Patients were asked if they had been hospitalized overnight for any reason during each three-month follow-up data collection period (or in the case of the Baseline Patient Questionnaire, during the period between initial hospital discharge and three months posttransplant). Responses to this question are shown in Tables 7-24 and 7-25 for patients grouped by initial immunosuppressive protocol and primary renal diagnosis, respectively.

In general, patients reported slightly fewer hospital stays than were reported by data collectors from the transplant centers. Less than one-half of all patients who responded to the survey (43.4%) reported that they had been hospitalized at least once during the period between initial hospital discharge and three months posttransplant. This figure is only slightly lower than the 49.7 percent which was reported by data collectors at the transplant centers. The information on hospital utilization provided by transplant patients also showed that hospital utilization decreases with increasing time

Table 7-24
Number of Disability Days and Number of Times Hospitalized During Patient Follow-up by Initial Immunosuppressive Protocol

	Discharge to 3 Months Posttransplant		3-6 Months Posttransplant		6-9 Months Posttransplant		9-12 Months Posttransplant		12-15 Months Posttransplant	
	AZA+PRED+ALG	CSA+PRED	AZA+PRED+ALG	CSA+PRED	AZA+PRED+ALG	CSA+PRED	AZA+PRED+ALG	CSA+PRED	AZA+PRED+ALG	CSA+PRED
Number of Disability Days										
0 Days (%)	74.6	68.3	83.4	79.7	72.6	84.2	80.4	86.8	66.7	84.2
1-2 Days (%)	4.7	4.9	3.7	4.3	7.4	8.8	3.9	2.6	9.1	5.3
3-5 Days (%)	5.3	6.1	4.9	2.9	6.3	3.5	7.8	5.3	6.1	5.3
6-10 Days (%)	8.9	9.8	3.7	4.3	7.4	1.8	5.9	2.6	3.0	5.3
11-15 Days (%)	3.0	3.7	0.6	2.9	3.2	0.0	2.0	2.6	6.1	0.0
16 or More Days (%)	3.6	7.3	3.7	4.3	2.1	1.8	0.0	0.0	9.1	0.0
Don't Know (%)	0.0	0.0	0.0	1.4	1.1	0.0	0.0	0.0	0.0	0.0
Number of Times Hospitalized										
0 Times (%)	59.2	51.2	79.8	64.7	78.9	84.2	88.2	86.8	84.3	78.9
1 Time (%)	26.0	37.8	16.6	29.4	16.8	12.3	5.9	13.2	18.8	10.5
2 Times (%)	12.4	9.8	3.1	5.9	3.2	1.8	5.9	0.0	0.0	5.3
3 Times (%)	2.4	1.2	0.6	0.0	1.1	1.8	0.0	0.0	0.0	5.3

Table 7-25
Number of Disability Days and Number of Times Hospitalized During Patient Follow-up by Primary Renal Diagnosis

	Discharge to 3 Months Posttransplant		3-6 Months Posttransplant		6-9 Months Posttransplant		9-12 Months Posttransplant		12-15 Months Posttransplant	
	Nondiabetes	Diabetes	Nondiabetes	Diabetes	Nondiabetes	Diabetes	Nondiabetes	Diabetes	Nondiabetes	Diabetes
Number of Disability Days										
0 Days (%)	69.4	81.5	83.1	80.0	77.2	76.3	84.3	78.9	70.0	83.3
1-2 Days (%)	4.3	6.2	4.5	1.8	7.9	7.9	4.3	0.0	10.0	0.0
3-5 Days (%)	5.9	4.6	4.5	3.6	5.3	5.3	5.7	10.5	7.5	0.0
6-10 Days (%)	10.2	6.2	3.4	5.5	4.4	7.9	4.3	5.3	2.5	8.3
11-15 Days (%)	4.3	0.0	1.1	1.8	2.6	0.0	1.4	5.3	5.0	0.0
16 or More Days (%)	5.9	1.5	2.8	7.3	2.6	0.0	0.0	0.0	5.0	8.3
Don't Know (%)	0.0	0.0	0.6	0.0	0.0	2.6	0.0	0.0	0.0	0.0
Number of Times Hospitalized										
0 Times (%)	57.0	55.4	77.3	69.1	85.0	69.2	91.3	75.0	87.2	58.3
1 Time (%)	27.4	36.9	19.3	23.6	12.4	23.1	7.2	15.0	10.3	33.3
2 Times (%)	12.9	7.7	2.8	7.3	1.8	5.1	1.4	10.0	2.6	0.0
3 Times (%)	2.7	0.0	0.6	0.0	0.9	2.6	0.0	0.0	0.0	8.3

since transplantation. During the period from 12 to 15 months posttransplant, only 24.1 percent of the patients who were surveyed indicated that they had been hospitalized at least once. As shown in Table 7-25, diabetic patients also reported being hospitalized more frequently during the follow-up data collection period than did nondiabetic patients. These figures are consistent with the information as reported by the data collectors at the transplant centers.

Finally, as part of the Baseline and Follow-up Patient Questionnaires patients were asked to provide information on the number of days, if any, that they stayed home in bed because of any illness or injury (that is, the number of disability days) during each follow-up data collection period. Overall, 27.9 percent of all patients indicated that they had stayed home in bed because of illness or injury during the period between initial hospital discharge and three months posttransplant. Patients who said that they had stayed in bed for all or most of the day at least once during their first three months posttransplant generally had 10 or fewer disability days during this time period. However, approximately eight percent of all patients included in the study reported more than 10 disability days. As can be seen in Table 7-24, patients who initially received CSA + PRED were more likely to say that they stayed at home in bed during this period of time than were patients who initially received AZA + PRED + ALG. Surprisingly, during this particular period of time diabetic patients were less likely than nondiabetic patients to report that they spent one or more days at home in bed (Table 7-25).

It is also interesting to note that the percentage of patients reporting one or more disability days during the subsequent follow-up periods does not decline with increasing time since transplantation. The percentage of patients reporting one or more disability days decreased from 27.9 percent for the period between hospital discharge and three months posttransplant to 18.1 percent for the period between three and six months posttransplant, then increased to 23.0 percent for the period between six and nine months posttransplant. During the period between 9 and 12 months posttransplant, the percentage of patients with one or more disability days decreased again to 16.9 percent and then increased to 26.9 percent for the period between 12 and 15 months posttransplant. Also, no consistent pattern in the relationship between disability days and initial immunosuppressive protocol or primary renal diagnosis is apparent.

Discussion

In this chapter we examined various clinical outcomes of patients following transplant surgery. The specific outcomes examined include renal function, adverse reactions to cyclosporine, disease symptomatology and other posttransplant complications, and hospitalizations and disability days in the months following transplantation. Clinical outcomes were measured at several points in time--at 3-months, 6-months, 9-months, 12-months, and 15-months posttransplant. Differences in the various clinical outcomes were examined separately for patients in the two initial immunosuppressive protocol groups (AZA + PRED + ALG versus CSA + PRED), and for patients grouped by primary renal diagnosis (diabetes versus nondiabetes).

The results of our analysis revealed that patients who initially received AZA + PRED + ALG had better renal function following transplantation than did patients who initially received CSA + PRED. Patients who initially received CSA + PRED had higher serum creatinine levels than patients who initially received AZA + PRED + ALG for as long as 15 months following transplant surgery and CSA + PRED patients experienced more episodes of renal dysfunction than did AZA + PRED + ALG patients during the first six months posttransplant. The renal function of both initial immunosuppressive protocol groups improved with increasing time since transplantation. Neither the number of episodes of renal dysfunction nor serum creatinine levels, however, differed by primary renal diagnosis.

Participating transplant patients experienced a number of adverse reactions to their cyclosporine therapy in the months following their transplant surgery. The two most commonly reported side-effects were tremors and hypertension. Diabetic and nondiabetic patients were equally likely to experience most of the adverse reactions to cyclosporine. However, the extent to which patients experienced adverse reactions to cyclosporine varied greatly depending upon when the cyclosporine therapy was begun. Patients who initially received CSA + PRED experienced more adverse reactions to cyclosporine compared with patients who initially received AZA + PRED + ALG. This no doubt reflects the fact that CSA + PRED patients initially received much higher dosages of cyclosporine than AZA + PRED + ALG patients. With the exception of hypertension, the negative side-effects of cyclosporine therapy decreased with increasing time since transplantation (as dosages of cyclosporine were gradually reduced).

In general, transplant patients reported that they frequently experienced a rather large number of symptoms and health-related problems prior to receiving their transplant. With the exception of problems associated with their immunosuppressive therapy (i.e., tremors, muscle weakness, extra body hair growth) patients reported fewer symptoms and health-related problems following transplantation when compared with prior to their transplant surgery. With the exception of various adverse reactions to cyclosporine, which decreased somewhat with increasing time since transplantation, the frequency of most symptoms reported remained relatively constant over time. With the passage of time, the dosages of cyclosporine were reduced for both groups and, as a result, fewer negative side-effects were reported by all patients. However, based on information obtained from the patients medical records, CSA + PRED patients consistently experience more hypertension than AZA + PRED + ALG patients in the months following transplantation. Although diabetic patients were more likely than nondiabetic patients to say that they often experienced various symptoms and health-related problems prior to transplantation, the two groups did not differ in the frequency of symptoms and health-related problems following transplantation.

Finally, we examined hospital utilization of the patients in the months following their transplant surgery. Neither hospital utilization in the year prior to transplantation nor hospital utilization in the first 15 months posttransplant varied by initial immunosuppressive protocol. Diabetic patients were hospitalized more often than nondiabetic patients in the year prior to transplantation and, in the months following transplantation, diabetic patients continued to be hospitalized more often than nondiabetic patients. Hospital utilization for both groups decreased with increasing time since transplantation. With respect to information on hospitalizations during the various follow-up data collection periods, information reported by patients was remarkably similar to information provided by transplant center staff.

CHAPTER 8

EMPLOYMENT, WORK DISABILITY, AND INCOME SUPPORT PROGRAM PARTICIPATION

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Introduction

For many people with chronic illness, the ability to work either at home or in the paid labor force is a major consideration in evaluating their quality of life. The impact of disease on the ability to work obviously depends on the nature and extent of the disease, as well as on the nature of the work to be performed. Although end-stage renal disease (ESRD) is a chronic and severe illness with high treatment costs, it may, but does not always, limit the patient's ability to work. Many kidney dialysis and transplant patients continue to work and function socially very much as they did prior to the onset of the disease (Flechner et al., 1983:572; Flores and Callender, 1987:115; Martino, 1987:107; Richardson, 1987:111; Simmons et al., 1988:481). Yet, there are some people for whom the disease is totally debilitating. For the vast majority of patients, ESRD imposes limitations on activity but does not totally rule out work or other social activities.

Many end-stage renal disease patients find that while on dialysis they are unable to participate in the labor force for a variety of reasons, including time problems and physical limitations. Because kidney transplant patients do not face the constraint of three dialysis sessions per week, they have more time available to devote to labor market activity. This, one would assume, would tend to encourage labor force participation. Indeed, one of the advantages often cited in favor of kidney transplantation, when compared with maintenance hemodialysis in the treatment of ESRD, is in its potential for allowing patients to return to work. In this regard, the research of Simmons and Callender (1988:481), as well as our own, is particularly noteworthy. Table 8-1 summarizes the vocational rehabilitation of male end-stage renal disease patients by treatment group from an ongoing study under

Table 8-1
Vocational Rehabilitation of Male End-Stage Renal Disease Patients by Treatment Group

Patient Status	In-Center Hemodialysis (43 Patients)	CAPD (254 Patients)	Current Transplant (59 Patients)	Historical Transplant (40 Patient
Proportion full-time work or school	19%	35%	64%	75%
Proportion part-time work or school	11%	11%	15%	7%
Proportion not working or in school	70%	54%	20%	18%
	100%	100%	100%	100%

* According to a chi-square test, differences between groups are significant, ($p \leq 0.001$)

SOURCE: Simmons *et al*., 1988:481.

the direction of Simmons. As indicated, 80 percent or more of the transplant patients in their study are working or going to school either full-time or part-time, whereas the comparable figures for in-center hemodialysis patients and continuous ambulatory peritoneal dialysis patients are 30 percent and 46 percent, respectively. All patients in the study were nondiabetic, between the ages of 19 and 55 years, and had been on their respective therapies for at least one year.

The results of our research are somewhat less impressive than those reported by Simmons et al. We have found that far more kidney transplant recipients are able to work than are actually working (Evans et al., 1985:553; 1987), although kidney transplant recipients have a labor force participation rate that exceeds that of patients on any other ESRD treatment modality, as shown in Table 8-2. In our study, very few patients were enrolled in school (either full-time or part-time) and our analysis was not limited to males only.

Despite these unfavorable results, it is apparent from our previous research that for end-stage renal disease patients the decision to return to work is further complicated by the special status given to patients under the Medicare End-Stage Renal Disease Program. To date, end-stage renal disease is the only specific disease that the Federal Government covers under Medicare for those under 65 years of age. Under Medicare's disability program, end-stage renal disease is essentially treated as prima facie evidence of disability. As such, dialysis patients have a very high probability of receiving a disability entitlement if they seek it (Bean et al., 1980; National ESRD Rehabilitation Task Force, 1982). Obviously, for dialysis patients, being entitled to disability benefits when not working lessens the net gains to be derived from working.

Table 8-2
Ability to Work and Employment Status of Patients
in the National Kidney Dialysis and Kidney Transplant Study

Treatment Modality	Able to Work (Percent)	Actually Working (Percent)	Mean Age (Years)
Kidney Transplant	74.1	45.6	37.2
Home Hemodialysis	59.3	36.2	47.0
In-Center Hemodialysis	37.1	20.5	51.9
Continuous Peritoneal Dialysis	24.7	16.2	49.8

SOURCE: Evans et al., 1985:553, 1987.

Thus, the ability to work does not necessarily imply that a person will work. For a kidney transplant recipient, however, the decision to work may depend on many factors, such as what they can expect to gain from working (both the wages and nonpecuniary features), whether or not their spouse is employed, the availability of retirement and disability benefits, and whether or not they can find work in their usual occupation. Currently, kidney transplant patients continue to be eligible for Medicare benefits for up to three years following a successful transplant (and longer if they are determined to be disabled). When their Medicare benefits expire, transplant patients may have a greater incentive to return to the labor force--to pay for medical and other living expenses.

In this chapter we examine the employment and work disability of participating renal transplant patients in the months following their transplant surgery. We begin by first comparing the employment status of patients following surgery with their employment status during the year prior to transplantation. In addition to examining actual employment status, we evaluate the extent to which patients say that they are limited in their ability to work following transplantation. Finally, we examine whether or not transplant patients receive disability or retirement benefits from various sources.

Variables

Although the general meanings of the terms "health" and "disability" are probably clear to most researchers, in specific applications they are used almost interchangeably by some researchers and disciplines, but for others they are distinctly different. Nagi (1976:439; 1979:1) makes clear distinctions among the terms "pathology," "impairment," "functional limitations," and "disability." Briefly, he defines these terms as follows:

- Pathology is the existence of disease in an individual.
- Impairment is the subnormal functioning of a human body system because of the existence of disease.
- Functional limitations are the restrictions in the ability of an individual to carry out normal tasks because of the existence of impairment.
- Disability is "a form of inability or limitation in performing roles or tasks within a social environment." (Nagi, 1979:1)

Furthermore, Nagi has drawn a distinction between work disability and independent living disability. Work disability concerns limitations with regard to activities performed on the job, and independent living disability is relative to the more basic activity of daily living. It should be apparent from both the definitions and casual observation that the links among these concepts are approximate and not deterministic. That is, pathology does not imply impairment, nor does impairment necessarily imply functional limitations. As defined above, having work disability does not necessarily imply that an individual will not work, only that the probability of working will be lower.

The Baseline and Follow-up Patient Questionnaires provided information regarding the employment and work disability of transplant patients following their transplant surgery. As an indication of employment status, respondents were asked to indicate which of the following best described their work activity or employment status at the time of the survey:

1. Employed full-time.
2. Employed part-time.
3. Employed but temporarily laid off.
4. Unemployed, looking for work.
5. Unemployed, not looking for work.
6. Unable to work because of health (disabled).
7. Homemaker.
8. Student (full-time).

9. Retired.
10. Other.

Respondents were also asked which of the above categories best described their work activity or employment status during the year prior to receiving their kidney transplant.

The patient's ability to work was determined based on the answer to the question: "Are you **NOW ABLE** to work for pay full-time, part-time, or not at all?" Patients were also asked whether or not their health keeps them from working on a job for pay, and whether or not they are limited in the **KIND** of work and in the **AMOUNT** of work for pay they can do because of their health.

In addition, patients were asked a series of questions regarding whether or not they receive disability and retirement benefits from various public and private sources. Since out-of-pocket medical expenses (in particular, the costs associated with immunosuppressive drugs) can impose a significant burden on transplant recipients and their families, patients were asked if they have had any difficulty paying for their immunosuppressive medications, and if they receive any assistance in paying for immunosuppressive drugs. Finally, patients were asked if finances were a source of worry at the time of the transplant, as well as at several points in time following transplantation.

Results

Patients were asked a series of questions regarding their employment and work disability at several points in time following their transplant surgery--at 3-months, 6-months, 9-months, 12-months, and 15-months posttransplant. In addition, patients were asked about their employment status in the year prior to their kidney transplant. Differences in employment and work disability are examined separately for patients in the two initial immunosuppressive protocol groups (AZA + PRED + ALG versus CSA + PRED), as well as for patients grouped by primary renal diagnosis (diabetes versus nondiabetes). The longitudinal nature of the study design provides an opportunity to examine changes in the employment and work disability of participating transplant recipients over time. In addition, whenever possible the employment and work disability of participating transplant recipients is compared with other kidney dialysis and transplant patients.

Our discussion of results is divided into three sections. In the first section we examine differences in employment and work disability of transplant patients by initial immunosuppressive protocol, as well as by primary renal diagnosis. In this section we also compare the employment status of transplant patients three-months posttransplant with their employment status during the year prior to transplantation. In the second section we examine differences in employment and work disability at three-month intervals from 3 to 15 months posttransplant. The final section presents a comparison of participating transplant recipients with other kidney dialysis and transplant patients.

Differences by Initial Immunosuppressive Protocol and Primary Renal Diagnosis

In this section we examine several variables related to employment and work disability. These include: (1) employment status; (2) ability to work; and (3) disability and retirement benefits. The analysis presented here is descriptive. With the exception of initial immunosuppressive protocol and primary renal diagnosis, no attempt is made to consider other case-mix differences in examining the employment and work disability of renal transplant recipients following transplant surgery.

Employment Status--

Table 8-3 presents the employment status of participating transplant recipients during the year prior to transplant surgery and three months following surgery. As shown in the table, approximately one-half of patients (50.7%) reported that they were employed either full-time or part-time during the year prior to their surgery. However, three months after the surgery, only 28.7 percent of the patients were employed. Three months after the transplant surgery, the percentages of patients who reported that they were unable to work because of their health (34.6%), or who said that they were a homemaker (14.2%), were retired (5.9%) or were unemployed and looking for work (7.5%) were higher than for the year prior to the transplant surgery.

The employment status of patients in the two initial immunosuppressive protocol groups in the year prior to surgery and three-months posttransplant are shown in Table 8-4. Prior to their transplant surgery, the percentage of patients who were employed did not differ for the two initial immunosuppressive protocol groups. As shown in Table 8-4, 51.9 percent of AZA + PRED + ALG patients and 48.2 percent of CSA + PRED patients were employed either full-time or part-time in the year prior to receiving their kidney transplant. The percentages of patients who said that they were unable to work because of their health were also similar for the two groups (27.6% and 23.0% of AZA + PRED + ALG patients and CSA + PRED patients, respectively).

Three months following transplantation, patients who initially received CSA + PRED were somewhat more likely to be employed full-time or part-time than were patients who initially received AZA + PRED + ALG. Among

Table 8-3
Employment Status of Participating Renal Transplant Recipients During the Year Prior to Transplant Surgery and at Three Months Posttransplant

	Year Prior To Transplant	3 Months Posttransplant
Employed Full-Time (%)	40.8	22.8
Employed Part-Time (%)	9.9	5.9
Employed But Temporarily Laid off (%)	1.1	0.8
Unemployed, Looking for Work (%)	1.1	7.5
Unemployed, Not Looking for Work (%)	0.4	2.4
Unable to Work Because of Health (%)	26.1	34.6
Homemaker (%)	12.9	14.2
Full-Time Student (%)	3.7	3.1
Retired (%)	2.9	5.9
Other (%)	1.1	2.8
Number of Cases	272	254

Table 8-4
Employment Status of Participating Transplant Recipients During the Year Prior to Transplant Surgery and Three Months Posttransplant by Initial Immunosuppressive Protocol

	Year Prior To Transplant		3 Months Posttransplant	
	AZA+PRED+ALG	CSA+PRED	AZA+PRED+ALG	CSA+PRED
Employed Full-time (%)	40.0	42.5	21.6	25.3
Employed Part-time (5)	11.9	5.7	5.3	7.2
Employed but Temporarily Laid Off (%)	1.1	1.1	0.0	2.4
Unemployed, Looking for Work (%)	0.5	2.3	8.8	4.8
Unemployed, not Looking for Work (%)	0.5	0.0	2.3	2.4
Unable to Work Because of Health (%)	27.6	23.0	38.6	26.5
Homemaker (%)	10.3	18.4	11.1	20.5
Full-Time Student (%)	3.2	4.6	3.5	2.4
Retired (%)	3.2	2.3	5.8	6.0
Other (%)	1.6	0.0	2.9	2.4
Number of Cases	185	87	171	83

patients who initially received AZA + PRED + ALG, 26.9 percent were employed three months posttransplant, compared with 32.5 percent of patients who initially received CSA + PRED. Similarly, 38.6 percent of AZA + PRED + ALG patients said they were unable to work because of their health three months following transplant surgery, while only 26.5 percent of CSA + PRED patients said that they were disabled. When compared with AZA + PRED + ALG patients, a higher percentage of CSA + PRED patients said that they were homemakers three months posttransplant. However, this pattern was also observed during the year prior to their surgery.

Next, we compared the employment status during the year prior to surgery and three months posttransplant of patients grouped by primary renal diagnosis. As can be seen in Table 8-5, the employment status of patients three months following transplantation differs greatly for diabetic and nondiabetic patients. Most obvious is the fact that three months following transplantation, 53.8 percent of diabetic patients said that they were unable to work because of their health, while only 28.0 percent of nondiabetic patients said that they were disabled. Interestingly, the percentages of patients who were working full-time three-months posttransplant were similar for the two groups.

It is perhaps not too surprising to observe the difference in the employment status of diabetic and nondiabetic patients three months following transplantation, since the employment status of patients in the two groups differed during the year prior to their transplant surgery. During the year prior to transplantation, 54.1 percent of nondiabetic patients were employed either full-time or part-time and only 21.2 percent of nondiabetic patients said they were unable to work because of their health. In contrast, only 40.5

Table 8-5
Employment Status of Participating Transplant Recipients During the Year Prior to Transplant Surgery and at Three Months Posttransplant by Primary Renal Diagnosis

	Year Prior to Transplant		3 Months Posttransplant	
	Nondiabetes	Diabetes	Nondiabetes	Diabetes
Employed Full-time (%)	43.3	33.3	23.8	20.0
Employed Part-time (5)	10.8	7.2	7.4	1.5
Employed but Temporarily Laid Off (%)	0.5	2.9	1.1	0.0
Unemployed, Looking for Work (%)	1.0	1.4	9.0	3.1
Unemployed, not Looking for Work (%)	0.5	0.0	2.1	3.1
Unable to Work Because of Health (%)	21.2	40.6	28.0	53.8
Homemaker (%)	13.3	11.6	14.3	13.8
Full-Time Student (%)	4.4	1.4	3.7	1.5
Retired (%)	3.9	0.0	7.4	1.5
Other (%)	1.0	1.4	3.2	1.5
Number of Cases	203	69	189	65

percent of diabetic patients were employed and 40.6 percent of diabetic patients said they were disabled during the year prior to transplantation.

Table 8-6 presents a cross-tabulation of employment status three-months posttransplant with employment status during the year prior to transplantation. For the purposes of this table, the 10 employment status categories have been reduced to five employment categories. These include: (1) employed full-time or part-time; (2) unable to work because of health; (3) retired; (4) homemaker; and (5) other. It should be noted that the employed full-time and employed part-time categories have been combined. In addition, the "other" employment category shown in Table 8-6 combines the following employment categories: (1) employed but temporarily laid off; (2) unemployed, looking for work; (3) unemployed, not looking for work; (4) full-time student; and (5) other.

As shown in Table 8-6, the major change in employment status resulted from patients who were employed prior to transplantation moving to the disabled category, although a fairly large number of formerly employed patients entered the retired and the other "unemployed" categories. The formerly disabled patients typically remained disabled, with only one formerly disabled patient being employed three months posttransplant. Those patients who were retired or who were homemakers prior to transplantation tended to remain in these same categories three months following transplant surgery.

Ability to Work--

In addition to asking questions about their current employment status, all patients were asked a series of questions concerning their ability to work. Responses to these questions are summarized in Table 8-7. Patients were asked whether, three months following transplant surgery, they were able to

Table 8-6
Number of Participating Renal Transplant Recipients by Employment Status During the Year Prior to Transplant Surgery and at Three Months Posttransplant

Employment Status Prior to Transplantation	Employment Status 3 Months Posttransplant					
	Employed Full-Time or Part-Time	Unable to Work Because of Health	Retired	Homemaker	Other*	Total
Employed Full-Time or Part-Time	71	36	7	2	13	129
Unable to Work Because of Health	1	49	0	6	9	65
Retired	0	0	7	0	0	7
Homemaker	0	1	1	28	4	34
Other*	1	2	0	0	16	19
Total	73	88	15	36	42	254

*Other category includes those (1) employed but temporarily laid off; (2) unemployed, looking for work; (3) unemployed, not looking for work; (4) full-time students; and (5) others.

work for pay full-time, part-time, or not at all. Of the patients responding, 36.9 percent said they could work full-time and 17.7 percent said they could work part-time. The remaining 45.4 percent either could not work at all or were uncertain if they would be able to do so. When asked whether their health kept them from working on a job for pay, 53.8 percent of patients said that their health did keep them from working. Overall, 64.9 percent said that they were limited in the kind of work they could do and 59.0 percent said that they were limited in the amount of work they could do because of their health.

As shown in Table 8-7, the percentage of patients who said that they were able to work full-time three months following transplantation was similar for the two initial immunosuppressive protocol groups. However, a somewhat higher percentage of patients who initially received CSA + PRED indicated that they were able to work part-time than did patients who initially received AZA + PRED + ALG. Therefore, the percentage of patients who said that they were not able to work for pay was slightly higher for the AZA + PRED + ALG patient group.

Differences in the ability to work by primary renal diagnosis were much more apparent. Among nondiabetic patients, 40.8 percent said that they were able to work for pay full-time three months following transplant surgery. In contrast, only 26.2 percent of diabetic patients said that they were able to work full-time. Almost two-thirds of diabetic patients indicated that they were not able to work at all, compared with less than 40 percent of nondiabetic patients. Diabetic patients were also much more likely than nondiabetic patients to say that their health kept them from working on a

Table 8-7
Ability to Work of Participating Transplant Recipients Three Months Following Transplant Surgery by Initial Immunosuppressive Protocol and Primary Renal Diagnosis

	All	Primary Renal Diagnosis		Initial Immunosuppressive Protocol	
	Patients	Nondiabetes	Diabetes	AZA+PRED+ALG	CSA+PRED
Able to Work for Pay					
Full-Time (%)	36.9	40.8	26.2	36.9	37.0
Part-Time (%)	17.7	20.1	10.8	15.5	22.2
Not at all (%)	45.4	39.1	63.1	47.6	40.7
Health Prevents Working for Pay					
Yes (%)	53.8	47.9	70.8	57.3	46.3
No (%)	46.2	52.1	29.2	42.7	53.7
Limited in Kind of Work					
Yes (%)	64.9	58.6	83.1	62.7	69.5
No (%)	35.1	41.4	16.9	37.3	30.5
Limited in Amount of Work					
Yes (%)	59.0	55.4	69.2	57.6	61.7
No (%)	41.0	44.6	30.8	42.4	38.3

job for pay, that they were limited in the kind of work they could do because of their health, and that they were limited in the amount of work they could do because of their health.

Retirement and Disability Benefits--

Patients were asked to indicate whether or not they were receiving retirement or disability benefits from a number of public and private sources. A summary of the percentages of patients who reported receiving benefits from these sources three months following their transplant surgery, overall as well as by initial immunosuppressive therapy and primary renal diagnosis, is shown in Table 8-8. Clearly, three months following transplant surgery many patients were receiving some form of income support through a variety of programs, the most common source being Social Security Retirement or Disability benefits. Of the 254 patients who responded to this question, 43.5 percent were receiving Social Security Retirement or Disability benefits and 17.8 percent were receiving Supplemental Security Income. Similarly, 9.5 percent were receiving disability benefits and 5.1 percent were receiving retirement or pension benefits provided by unions or employers.

As we previously observed, three months following transplant surgery, patients who initially received CSA + PRED were somewhat more likely to be employed full-time or part-time than were patients who initially received AZA + PRED + ALG. Similarly, the percentage of patients who said that they were not able to work for pay three months posttransplant was higher among AZA + PRED + ALG patients than among CSA + PRED patients. Therefore, it is not surprising to observe that three months following transplantation, a higher percentage of AZA + PRED + ALG patients were receiving Social

Table 8-8
Percent of Patients Receiving Retirement and Disability Benefits Three Months Following Transplant Surgery by Initial Immunosuppressive Protocol and Primary Renal Diagnosis

	All Patients	Primary Renal Diagnosis		Initial Immunosuppressive Protocol	
		Nondiabetes	Diabetes	AZA+PRED+ALG	CSA+PRED
Social Security Retirement or Disability Benefits (Green Check) (%)	43.5	39.9	53.8	47.4	35.4
Supplemental Security Income (SSI) (Gold Check) (%)	17.8	18.6	15.4	18.1	17.1
Railroad Retirement Benefits (%)	0.0	0.0	0.0	0.0	0.0
Veterans Administration Benefits (%)	1.6	1.1	3.1	1.8	1.2
Unemployment Compensation (%)	0.8	0.5	1.5	1.2	0.0
Workmen's Compensation (%)	0.4	0.5	0.0	0.6	0.0
"Aid to Families with Dependent Children" (AFDC) Assistance (%)	2.8	1.6	6.2	2.9	2.4
Public Welfare or Assistance (%)	2.0	2.1	1.5	1.2	3.7
Civil Service Benefits (%)	2.0	2.7	0.0	2.3	1.2
Union or Employer Disability Benefits (%)	9.5	9.6	9.2	9.4	9.8
Union or Employer Retirement or Pension Benefits (%)	5.1	5.9	3.1	5.8	3.7
Any Other Benefits	2.8	3.2	1.5	2.9	2.4

Security Retirement or Disability benefits compared with CSA + PRED patients. A slightly higher percentage of AZA + PRED + ALG patients were also receiving union or employer retirement or pension benefits. However, the percentages of patients receiving the other benefits shown in Table 8-8 were similar for the two initial immunosuppressive protocol groups.

Also consistent with our previous findings, diabetic patients were much more likely than nondiabetic patients to be receiving Social Security Retirement or Disability benefits. As shown in Table 8-8, three months following transplant surgery, 39.9 percent of nondiabetic patients and 53.8 percent of diabetic patients were receiving Social Security Retirement or Disability benefits. The percentage of patients who were receiving "Aid to Families with Dependent Children" (AFDC) was also higher among diabetic patients. In contrast, the nondiabetic patients were somewhat more likely than diabetic patients to be receiving Supplemental Security Income (SSI) and union or employer retirement or pension benefits. The percentages of patients receiving the various other benefits did not differ by primary renal diagnosis.

Patients were also asked several questions regarding their financial concerns at the time of the survey, as well as at the time the transplant procedure was performed. Since out-of-pocket health care costs, and in particular the cost of outpatient immunosuppressive drugs, can impose a large financial burden on the transplant recipient, patients were asked if they have had any difficulty paying for their immunosuppressive medications. As shown in Table 8-9, three months following transplant surgery, only 22.8 percent of the patients responded "yes." Of the 57 patients who said that they did have difficulty paying for their drugs, 54 said that they had difficulty paying for cyclosporine, 14 said that they had difficulty paying for prednisone (or other steroids), and four said that they had difficulty paying for azathioprine. Patients were also asked if they currently (i.e., three months posttransplant) receive any assistance in paying for their immunosuppressive drugs. An overwhelming 97.2 percent said that they received assistance in paying for their immunosuppressive drugs. Approximately two-thirds of all patients indicated that private insurance helped them pay for their immunosuppressive drugs. The next most commonly cited sources of assistance were Medicare, State Kidney Program and Medicaid. Patient responses did not vary by primary renal diagnosis or initial immunosuppressive protocol.

Finally, patients were asked about finances as a source of worry at the time of their transplant and at three months posttransplant. The responses to these questions are shown in Table 8-9. At the time of their kidney transplant, 21.8 percent of patients said that they were "extremely worried" and 26.2 percent said that they were "moderately worried " about finances. Only 21.8 percent said that they were "not at all worried." Clearly, finances continue to be a source of worry to most transplant recipients in the months following transplant surgery. As shown in Table 8-9, the level of worry over finances changed very little in the first three months after the transplant surgery.

While there was little difference in the responses of nondiabetic and diabetic patients concerning their level of worry over finances at the time of their transplant surgery, diabetic patients were more worried than nondiabetic patients three months posttransplant. With respect to initial immunosuppressive protocol, a more interesting pattern can be observed. The percentage of patients who reported being "extremely worried" about finances

Table 8-9
Financial Difficulties Experienced by Transplant Recipients at Time of Transplant and at Three Months Posttransplant by Initial Immunosuppressive Protocol and Primary Renal Diagnosis

	All Patients	Primary Renal Diagnosis		Initial Immunosuppressive Protocol	
		Nondiabetes	Diabetes	AZA+PRED+ALG	CSA+PRED
Have Difficulty Paying for Immunosuppressive Drugs					
Yes (%)	22.8	23.2	21.5	21.3	25.9
No (%)	77.2	76.8	78.5	78.7	74.1
Receive Assistance Paying for Drugs					
Yes (%)	97.2	96.8	98.5	97.1	97.6
No (%)	2.8	3.2	1.5	2.9	2.4
Worried About Finances at Time of Transplant					
Extremely Worried (%)	21.8	21.3	23.2	23.8	17.4
Moderately Worried (%)	26.2	26.2	26.1	23.8	31.4
A Little Worried (%)	30.3	31.2	27.5	29.2	32.6
Not at all Worried (%)	21.8	21.3	23.2	23.2	18.6
Worried About Finances Now					
Extremely Worried (%)	19.8	17.0	27.7	17.5	24.4
Moderately Worried (%)	30.8	31.9	27.7	32.7	26.8
A Little Worried (%)	27.7	26.1	32.3	28.7	25.6
Not at all Worried (%)	21.7	25.0	12.3	21.1	23.2

at the time of transplant was higher for those patients who initially received AZA + PRED + ALG than for patients who received CSA + PRED. However, a higher percentage of AZA + PRED + ALG patients also said that they were "not at all worried" about finances at the time of transplant compared with patients who initially received CSA + PRED. Three months following transplantation, the percentage of patients who reported being "extremely worried" about finances was higher among CSA + PRED patients compared with patients who initially received AZA + PRED + ALG. The percentage of CSA + PRED patients who said that they were "not at all worried" about finances three months posttransplant was also higher than the percentage of CSA + PRED patients who said that they were "not at all worried" about finances at the time of transplant.

Changes in Employment and Work Disability Over Time

Having examined differences in employment and work disability by initial immunosuppressive protocol and primary renal diagnosis three months following transplant surgery, we now turn our attention to the question of whether or not transplant patients return to work in the months following transplantation. In addition to obtaining information concerning the employment and work disability of participating transplant patients three months following their transplant surgery, similar information was collected at 6, 9, 12, and 15 months posttransplant. Thus, we are able to examine the extent to which the employment status of transplant recipients changes over time.

Employment Status--

In the previous section of this chapter, we observed that fewer transplant patients were employed either full-time or part-time three months following their transplant surgery than were employed in the year prior to transplantation. Similarly, transplant patients were more likely to report that they were disabled three months posttransplant than in the year prior to receiving their transplant. However, for many patients three months may represent a normal period of recuperation following major surgery. By examining employment status at three-month intervals following surgery we will determine whether or not this decrease in labor force participation is temporary, or if it continues beyond the first three months posttransplant.

Table 8-10 presents the employment status of participating transplant recipients during the year prior to transplant surgery, as well as at 3, 6, 9, 12, and 15 months posttransplant. As noted earlier, only 28.7 percent of patients were employed either full-time or part-time and 34.6 percent of patients reported that they were disabled three months following their transplant surgery. By nine months posttransplant, a somewhat higher percentage of patients were employed either full-time or part-time (33.6%); however, the percentage of patients who said they were disabled (33.6%) was approximately the same as at three months posttransplant. At 12 and 15 months following transplantation, the percentage of patients who were employed increased to 39.4 percent and 43.1 percent, respectively. And, the percentage of patients who reported being disabled was 28.1 percent at 12 months posttransplant and 23.5 percent at 15 months posttransplant. It is somewhat difficult to draw conclusions based on the data for these later time periods because the number of patients for whom employment status was

Table 8-10
Employment Status of Participating Renal Transplant Recipients During the Year Prior to Transplant Surgery And at 3, 6, 9, 12 and 15 Months Posttransplant

Employment Status	Prior to Transplant	Posttransplant				
		3 Months	6 Months	9 Months	12 Months	15 Months
Employed Full-Time (%)	40.8	22.8	29.4	27.0	31.5	35.3
Employed Part-Time (%)	9.9	5.9	6.9	6.6	7.9	7.8
Employed But Temporarily Laid Off (%)	1.1	0.8	0.4	0.0	1.1	0.0
Unemployed, Looking For Work (%)	1.1	7.5	5.6	7.9	3.4	0.0
Unemployed, Not Looking For Work (%)	0.4	2.4	1.7	1.3	2.2	0.0
Unable to Work Because of Health (%)	26.1	34.6	31.2	33.6	28.1	23.5
Homemaker (%)	12.9	14.2	11.7	15.8	14.6	21.6
Full-Time Student (%)	3.7	3.1	4.8	2.6	6.7	5.9
Retired (%)	2.9	5.9	7.4	4.6	4.5	3.9
Other (%)	1.1	2.8	0.9	0.7	0.0	2.0
Number of Cases	272	254	231	152	89	51

known was small (89 in the case of the 12 month follow-up survey and 51 in the case of the 15 month follow-up survey). It is, however, interesting to note that, even 15 months following their transplant surgery, the percentage of patients who were employed either full-time or part-time was lower than the percentage of patients who were employed during the year prior to transplantation.

Table 8-11 presents the employment status of participating renal transplant recipients at 3, 6, 9, 12, and 15 months posttransplant by initial immunosuppressive protocol. Table 8-12 presents similar information for patients grouped by primary renal diagnosis. With respect to employment status during the months following transplant surgery the two initial immunosuppressive protocol groups appear to be quite similar. The percentage of patients who are employed either full-time or part-time is remarkably similar when measured at 6, 9 and 12 months following transplantation. Patients who initially received AZA + PRED + ALG were more likely to report being disabled, while patients who initially received CSA + PRED were more likely to say that they were homemakers. This was true during each of the follow-up time periods.

When the employment status of diabetic and nondiabetic patients is examined, however, some interesting differences are apparent. As shown in Table 8-12, the percentage of nondiabetic patients who were employed increased slightly over time, from 31.2 percent at three months posttransplant to 37.7 percent at nine months posttransplant. Although based on a very small number of patients, the percentage of nondiabetic patients who were employed was even higher 12 and 15 months following transplant surgery. The percentage of diabetic patients who were employed--which was

Table 8-11

Employment Status of Participating Transplant Recipients 3, 6, 9, 12 and 15 Months Posttransplant by Initial Immunosuppressive Protocol

	3 Months Posttransplant		6 Months Posttransplant		9 Months Posttransplant		12 Months Posttransplant		15 Months Posttransplant	
	AZA+PRED+ALG	CSA+PRED	AZA+PRED+ALG	CSA+PRED	AZA+PRED+ALG	CSA+PRED	AZA+PRED+ALG	CSA+PRED	AZA+PRED+ALG	CSA+PRED
Employed Full-Time (%)	21.6	25.3	28.2	32.4	25.3	29.8	33.3	28.9	34.4	36.8
Employed Part-Time (%)	5.3	7.2	7.4	5.9	8.4	3.5	5.9	10.5	12.5	0.0
Employed but Temporarily Laid Off (%)	0.0	2.4	0.0	1.5	0.0	0.0	2.0	0.0	0.0	0.0
Unemployed, Looking for Work (%)	8.8	4.8	6.1	4.4	6.3	10.5	3.9	2.6	0.0	0.0
Unemployed, Not Looking for Work (%)	2.3	2.4	1.8	1.5	1.1	1.8	0.0	5.3	0.0	0.0
Unable to Work Because of Health (%)	38.6	26.5	35.6	20.6	40.0	22.8	35.3	18.4	31.3	10.5
Homemaker (%)	11.1	20.5	9.2	17.6	12.6	21.1	7.8	23.7	12.5	36.8
Full-Time Student (%)	3.5	2.4	5.5	2.9	2.1	3.5	9.8	2.6	6.3	5.3
Retired (%)	5.8	6.0	4.9	13.2	3.2	7.0	2.0	7.9	0.0	10.5
Other (%)	2.9	2.4	1.2	0.0	1.1	0.0	0.0	0.0	3.1	0.0

Table 8-12
Employment Status of Participating Transplant Recipients 3, 6, 9, 12 and 15 Months Posttransplant by Primary Renal Diagnosis

	3 Months Posttransplant		6 Months Posttransplant		9 Months Posttransplant		12 Months Posttransplant		15 Months Posttransplant	
	Nondiabetes	Diabetes	Nondiabetes	Diabetes	Nondiabetes	Diabetes	Nondiabetes	Diabetes	Nondiabetes	Diabetes
Employed Full-Time (%)	23.8	20.0	31.3	23.6	29.8	18.4	35.7	15.8	41.0	16.7
Employed Part-Time (%)	7.4	1.5	8.0	3.6	7.9	2.6	7.1	10.5	7.7	8.3
Employed but Temporarily Laid Off (%)	1.1	0.0	0.6	0.0	0.0	0.0	1.4	0.0	0.0	0.0
Unemployed, Looking for Work (%)	9.0	3.1	5.1	7.3	7.9	7.9	1.4	10.5	0.0	0.0
Unemployed, Not Looking for Work (%)	2.1	3.1	2.3	0.0	0.9	2.6	1.4	5.3	0.0	0.0
Unable to Work Because of Health (%)	28.0	53.8	25.0	50.9	27.2	52.6	24.3	42.1	17.9	41.7
Homemaker (%)	14.3	13.8	13.1	7.3	16.7	13.2	14.3	15.8	17.9	33.3
Full-Time Student (%)	3.7	1.5	5.7	1.8	3.5	0.0	8.6	0.0	7.7	0.0
Retired (%)	7.4	1.5	7.9	5.5	5.3	2.6	5.7	0.0	5.1	0.0
Other (%)	3.2	1.5	1.1	0.0	0.9	0.0	0.0	0.0	2.6	0.0

considerably lower than the corresponding percentage among nondiabetic patients--remained relatively constant over time. For example, nine months following transplantation 37.7 percent of nondiabetic patients were employed compared with only 21.0 percent of diabetic patients. For both diabetic and nondiabetic patients, the percentage of patients who reported that they were disabled remained fairly constant over time. During the first 15 months posttransplant, neither diabetic patients nor nondiabetic patients achieved the same level of employment as was reported during the year prior to receiving their kidney transplant.

Finally, in Tables 8-13 through 8-16 we present cross-tabulations of employment status during the year prior to transplant surgery with employment status at 6, 9, 12, and 15 months posttransplant. Again, we have reduced the 10 employment status categories into the following five categories: employed full-time or part-time, unable to work because of health; retired; homemaker; and other. Clearly, the patients who were employed following their transplant surgery are those patients who were employed in the year prior to transplantation. As shown in Table 8-13, of the 84 patients who were employed six months posttransplant, 79 of these patients were employed prior to transplantation. Only two patients who said that they were disabled prior to transplantation were employed either full-time or part-time six months following their transplant surgery. Similarly, it is important to note that many patients who were employed in the year prior to transplantation reported being unable to work because of their health in the months following their transplant surgery. As shown in Table 8-13, a total of 119 patients reported that they were employed either full-time or part-time prior to transplantation. Of these 119 patients, 26 reported that

Table 8-13
Number of Participating Renal Transplant Recipients by Employment Status During the Year Prior to Transplant Surgery and at Six Months Posttransplant

	Employment Status 6 Months Posttransplant					
Employment Status Prior to Transplantation	Employed Full-Time or Part-Time	Unable to Work Because of Health	Retired	Homemaker	Other*	Total
Employed Full-Time or Part-Time	79	26	7	2	5	119
Unable to Work Because of Health	2	38	3	3	13	59
Retired	0	1	6	0	0	7
Homemaker	0	2	0	21	5	28
Other*	3	3	0	0	8	14
Total	84	70	16	26	31	227

*Other category includes those (1) employed but temporarily laid off; (2) unemployed, looking for work; (3) unemployed, not looking for work; (4) full-time students; and (5) others.

Table 8-14

Number of Participating Renal Transplant Recipients by Employment Status During the Year Prior to Transplant Surgery and at Nine Months Posttransplant

	Employment Status 9 Months Posttransplant					
Employment Status Prior to Transplantation	Employed Full-Time or Part-Time	Unable to Work Because of Health	Retired	Homemaker	Other*	Total
Employed Full-Time or Part-Time	47	18	4	2	3	74
Unable to Work Because of Health	2	28	1	3	6	40
Retired	0	2	2	0	0	4
Homemaker	0	1	0	18	1	20
Other*	2	1	0	1	9	13
Total	51	50	7	24	19	151

*Other category includes those (1) employed but temporarily laid off; (2) unemployed, looking for work; (3) unemployed, not looking for work; (4) full-time students; and (5) others.

Table 8-15
Number of Participating Renal Transplant Recipients by Employment Status During the Year Prior to Transplant Surgery and at 12 Months Posttransplant

	Employment Status 12 Months Posttransplant					
Employment Status Prior to Transplantation	Employed Full-Time or Part-Time	Unable to Work Because of Health	Retired	Homemaker	Other*	Total
Employed Full-Time or Part-Time	30	9	2	1	3	45
Unable to Work Because of Health	3	14	0	2	4	23
Retired	0	1	2	0	0	3
Homemaker	0	0	0	10	2	12
Other*	2	1	0	0	2	5
Total	35	25	4	13	11	88

*Other category includes those (1) employed but temporarily laid off; (2) unemployed, looking for work; (3) unemployed, not looking for work; (4) full-time students; and (5) others.

Table 8-16
Number of Participating Renal Transplant Recipients by Employment Status During the Year Prior to Transplant Surgery and at 15 Months Posttransplant

	Employment Status 15 Months Posttransplant					
Employment Status Prior to Transplantation	Employed Full-Time or Part-Time	Unable to Work Because of Health	Retired	Homemaker	Other*	Total
Employed Full-Time or Part-Time	18	4	1	1	2	26
Unable to Work Because of Health	3	6	0	3	0	12
Retired	0	1	1	0	0	2
Homemaker	0	0	0	7	0	7
Other*	1	1	0	0	2	4
Total	22	12	2	11	4	51

*Other category includes those (1) employed but temporarily laid off; (2) unemployed, looking for work; (3) unemployed, not looking for work; (4) full-time students; and (5) others.

they were disabled six months posttransplant, seven said they were retired, two were homemakers and five were classified as "other." Of the 59 patients who said that they were disabled prior to transplantation, 38 also reported being disabled six months posttransplant. However, a relatively large group of patients (13) were disabled prior to transplantation, but were classified in the "other" category six months following surgery (7 of these 13 patients were unemployed, looking for work). Based on these data it would appear that kidney transplantation is not particularly effective in allowing formerly disabled patients to return to work. As can be seen in Tables 8-14 through 8-16, these same patterns are apparent at 9, 12, and 15 months posttransplant.

Ability to Work--

In addition to asking patients about their ability to work three months following their transplant surgery, patients were also asked about their ability to work at 6, 9, 12, and 15 months posttransplant. Patient responses to these questions are summarized in Table 8-17. Clearly, there is an improvement in the ability of transplant patients to work on a job for pay in the first 15 months following their transplant surgery. The percentage of patients who said they were able to work for pay on a part-time basis did not change over time. However, the percentage of patients who said that they were able to work for pay on a full-time basis rose from 36.9 percent at three months posttransplant to 47.1 percent at 15 months posttransplant. The percentage of patients who said that they were not able to work at all declined from 45.4 percent to 33.3 percent during the same period of time. Similarly, the percentage of patients who said that their health kept them from working for

Table 8-17
Ability to Work of Participating Transplant Recipients at 3, 6, 9, 12 and 15 Months Posttransplant

	Number of Months Posttransplant				
	3 Months	6 Months	9 Months	12 Months	15 Months
Able to Work for Pay					
Full-Time (%)	36.9	42.9	40.1	50.6	47.1
Part-Time (%)	17.7	19.5	20.4	15.7	19.6
Not at All (%)	45.4	37.7	39.5	33.7	33.3
Health Keeps From Working for Pay					
Yes (%)	53.8	43.5	43.0	40.4	33.3
No (%)	46.2	56.5	57.0	59.6	66.7
Limited in Kind of Work					
Yes (%)	64.9	61.1	62.3	59.6	58.8
No (%)	35.1	38.9	37.7	40.4	41.2
Limited in Amount of Work					
Yes (%)	59.0	58.4	55.9	56.2	56.9
No (%)	41.0	41.6	44.1	43.8	43.1

pay decreased from 53.8 percent at three months posttransplant to 33.3 percent at 15 months posttransplant. Interestingly, however, even 15 months after receiving their kidney transplants, the majority of transplant patients still reported that they were limited in the kind of work and in the amount of work that they could do because of their health. As shown in Table 8-17, the percentage of patients who said that they were limited in the kind of work that they could do decreased only slightly, from 64.9 percent to 58.8 percent during the period between 3 and 15 months following transplantation. The percentage of patients who said that they were limited in the amount of work that they could do remained virtually unchanged over time.

Earlier we observed that there were no major differences between the two initial immunosuppressive protocol groups in the reported ability of transplant patients to work three months following their surgery. As can be seen in Table 8-18, in general, this same pattern persists over time. With respect to primary renal diagnosis, however, greater differences were apparent. Three months following transplant surgery, diabetic patients were much more likely than nondiabetic patients to say that they were unable to work at all. Diabetic patients were also more likely than nondiabetic patients to say that their health kept them from working on a job for pay, that they were limited in the kind of work that they could do because of their health, and that they were limited in the amount of work that they could do because of their health. As shown in Table 8-19, following transplantation both diabetic and nondiabetic patients improved with respect to their ability to work with the passage of time. The improvement was particularly dramatic in the case of the diabetic patient group. For example, three months following transplantation, 47.9 percent of nondiabetic patients and 70.8

Table 8-18

Ability to Work of Participating Transplant Recipients at 3, 6, 9, 12 and 15 Months Posttransplant by Initial Immunosuppressive Protocol

	3 Months Posttransplant		6 Months Posttransplant		9 Months Posttransplant		12 Months Posttransplant		15 Months Posttransplant	
	AZA+PRED+ALG	CSA+PRED	AZA+PRED+ALG	CSA+PRED	AZA+PRED+ALG	CSA+PRED	AZA+PRED+ALG	CSA+PRED	AZA+PRED+ALG	CSA+PRED
Able to Work for Pay										
Full-Time (%)	36.9	37.0	42.9	42.6	40.0	40.4	52.9	47.4	46.9	47.4
Part-Time (%)	15.5	22.2	19.6	19.1	15.8	28.1	9.8	23.7	15.6	26.3
Not at all (%)	47.6	40.7	37.4	38.2	44.2	31.6	37.3	28.9	37.5	26.3
Health Keeps From Working for Pay										
Yes (%)	57.3	46.3	46.0	37.7	48.9	33.3	45.1	34.2	34.4	31.6
No (%)	42.7	53.7	54.0	62.3	51.1	66.7	54.9	65.8	65.6	68.4
Limited in Kind of Work										
Yes (%)	62.7	69.5	60.2	63.2	61.7	63.2	58.8	60.5	65.6	47.4
No (%)	37.3	30.5	39.8	36.8	38.3	36.8	41.2	39.5	34.4	52.6
Limited in Amount of Work										
Yes (%)	57.6	61.7	58.9	57.4	55.8	56.1	52.9	60.5	59.4	52.6
No (%)	42.4	38.3	41.1	42.6	44.2	43.9	47.1	39.5	40.6	47.4

Table 8-19
Ability to Work of Participating Transplant Recipients at 3, 6, 9, 12, and 15 Months Posttransplant by Primary Renal Diagnosis

	3 Months Posttransplant		6 Months Posttransplant		9 Months Posttransplant		12 Months Posttransplant		15 Months Posttransplant	
	Nondiabetes	Diabetes	Nondiabetes	Diabetes	Nondiabetes	Diabetes	Nondiabetes	Diabetes	Nondiabetes	Diabetes
Able to Work for Pay										
Full-Time (%)	40.8	26.2	46.6	30.9	44.7	26.3	55.7	31.6	53.8	25.0
Part-Time (%)	20.1	10.8	21.6	12.7	21.9	15.8	14.3	21.1	12.8	41.7
Not At All (%)	39.1	63.1	31.8	56.4	33.3	57.9	30.0	47.4	33.3	33.3
Health Keeps From Working for Pay										
Yes (%)	47.9	70.8	38.4	60.0	36.3	63.2	37.1	52.6	30.8	41.7
No (%)	52.1	29.2	61.6	40.0	63.7	36.8	62.9	47.4	29.2	58.3
Limited in Kind of Work										
Yes (%)	58.6	83.1	56.3	76.4	58.4	73.7	54.3	78.9	51.3	83.3
No (%)	41.4	16.9	43.7	23.6	41.6	26.3	45.7	21.1	48.7	16.7
Limited in Amount of Work										
Yes (%)	55.4	69.2	54.5	70.9	51.8	68.4	51.4	73.7	48.7	83.3
No (%)	44.6	30.8	45.5	29.1	48.2	31.6	48.6	26.3	51.3	16.7

percent of diabetic patients said that their health kept them from working for pay. Fifteen months following transplantation, only 30.8 percent of nondiabetic patients and 41.7 percent of diabetic patients said that their health kept them from working. However, despite the improvement in the ability to work experienced by diabetic patients, at each point in time diabetic patients remain much more limited in their ability to work when compared with nondiabetic patients.

Retirement and Disability Benefits--

Table 8-20 shows the percentage of patients receiving various retirement and disability benefits at 3, 6, 9, 12, and 15 months posttransplant. As we reported earlier, a relatively high percentage of participating transplant patients receive some form of income support, with Social Security Retirement or Disability Benefits and Supplemental Security Income (SSI) being the most common benefits received. It is interesting that the percentage of patients receiving disability and retirement benefits varied little in the first 15 months posttransplant. For example, 43.5 percent of all patients were receiving Social Security Benefits and 17.8 percent of all patients were receiving SSI benefits three months following transplantation. Twelve months posttransplant, 42.7 percent of those patients surveyed were receiving Social Security Benefits and 16.9 percent of the patients were receiving SSI benefits. Although based on a relatively small number of patients, slightly lower percentages of patients reported receiving Social Security Retirement benefits and union or employer disability benefits 15 months following their transplant surgery.

Table 8-20
Percent of Patients Receiving Retirement and Disability Benefits at 3, 6, 9, 12, and 15 Months Posttransplant

	Number of Months Posttransplant				
	3 Months	6 Months	9 Months	12 Months	15 Months
Social Security Retirement or Disability Benefits (Green Check) (%)	43.5	43.5	44.4	42.7	38.5
Supplemental Security Income (SSI) (Gold Check) (%)	17.8	16.5	16.6	16.9	15.4
Railroad Retirement Benefits (%)	0.0	0.0	0.0	0.0	0.0
Veterans Administration Benefits (%)	1.6	1.7	0.0	1.1	3.8
Unemployment Compensation (%)	0.8	0.0	0.0	0.0	0.0
Workmen's Compensation (%)	0.4	0.0	0.0	0.0	0.0
"Aid to Families with Dependent Children" (AFDC) Assistance (%)	2.8	1.3	0.7	1.1	0.0
Public Welfare or Assistance (%)	2.0	1.7	1.3	1.1	1.9
Civil Service Benefits (%)	2.0	2.6	2.0	1.1	0.0
Union or Employer Disability Benefits (%)	9.5	5.7	9.3	5.6	1.9
Union or Employer Retirement or Pension Benefits (%)	5.1	7.4	5.3	6.7	1.9
Any Other Benefits	2.8	3.0	3.3	3.4	5.8

Earlier we observed that three months following transplantation, a higher percentage of AZA + PRED + ALG patients were receiving Social Security Retirement or Disability benefits (47.3%) compared with CSA + PRED patients (35.4%). As Table 8-21 shows, there is remarkably little variation in the percentage of patients receiving retirement and disability benefits over time for the two initial immunosuppressive protocol groups. Fifteen months following transplant surgery, 43.8 percent of patients who initially received AZA + PRED + ALG and only 31.6 percent of patients who initially received CSA + PRED reported that they were receiving Social Security Retirement or Disability benefits.

Table 8-22 presents the percent of participating transplant patients receiving various retirement and disability benefits at 3, 6, 9, 12, and 15 months posttransplant by primary renal diagnosis. In examining employment status we observed that the percentage of nondiabetic patients who were employed increased slightly in the months following transplantation, while the percentage of diabetic patients who were employed remained relatively constant over time. As shown in Table 8-22, the percentage of nondiabetic patients who reported that they were receiving Social Security benefits also decreased slightly during the period from 3 to 15 months posttransplant, whereas for diabetic patients the percentage increased slightly during this same period of time. Clearly, with the passage of time, diabetic patients continue to be more likely than nondiabetic patients to be receiving Social Security Retirement and Disability benefits.

Finally, we examined the financial difficulties reported by transplant recipients in the months following their transplant surgery. As shown in Table 8-23, overall there was little change in these variables over time.

Table 8-21
Percent of Patients Receiving Retirement and Disability Benefits at 3, 6, 9, 12 and 15 Months Posttransplant by Immunosuppressive Protocol

	3 Months Posttransplant		6 Months Posttransplant		9 Months Posttransplant		12 Months Posttransplant		15 Months Posttransplant	
	AZA+PRED+ALG	CSA+PRED	AZA+PRED+ALG	CSA+PRED	AZA+PRED+ALG	CSA+PRED	AZA+PRED+ALG	CSA+PRED	AZA+PRED+ALG	CSA+PRED
Social Security Retirement or Disability Benefits (Green Check) (%)	47.3	35.4	45.3	39.1	45.3	42.9	43.1	42.1	43.8	31.6
Supplemental Security Income (SSI) (Gold Check) (%)	18.1	17.1	19.9	8.7	20.0	10.7	21.6	10.5	18.8	10.5
Railroad Retirement Benefits (%)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Veterans Administration Benefits (%)	1.8	1.2	1.9	1.4	0.0	0.0	0.0	2.6	3.1	5.3
Unemployment Compensation (%)	1.2	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Workmen's Compensation (%)	0.6	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
"Aid to Families with Dependent Children" (AFDC) Assistance (%)	2.9	2.4	1.2	1.4	0.0	1.8	0.0	2.6	0.0	0.0
Public Welfare or Assistance (%)	1.2	3.7	0.6	4.3	0.0	3.6	0.0	2.6	0.0	5.3
Civil Service Benefits (%)	2.3	1.2	3.1	1.4	3.2	0.0	2.0	0.0	0.0	0.0
Union or Employer Disability Benefits (%)	9.4	9.8	3.1	11.6	6.3	14.3	3.9	7.9	3.1	0.0
Union or Employer Retirement Pension Benefits (%)	5.8	3.7	6.8	8.7	4.2	7.1	5.9	7.9	3.1	0.0
Any Other Benefits	2.9	2.4	3.1	2.9	2.1	5.4	2.0	5.3	3.1	10.5

Table 8-22
Percent of Patients Receiving Retirement and Disability Benefits at 3, 6, 9, 12 and 15 Months Posttransplant by Primary Renal Diagnosis

	3 Months Posttransplant		6 Months Posttransplant		9 Months Posttransplant		12 Months Posttransplant		15 Months Posttransplant	
	Nondiabetes	Diabetes	Nondiabetes	Diabetes	Nondiabetes	Diabetes	Nondiabetes	Diabetes	Nondiabetes	Diabetes
Social Security Retirement or Disability Benefits (Green Check) (%)	39.9	53.8	39.4	56.4	38.9	60.5	37.1	63.2	33.3	58.3
Supplemental Security Income (SSI) (Gold Check) (%)	18.6	15.4	16.6	16.4	15.9	18.4	17.1	15.8	12.8	25.0
Railroad Retirement Benefits (%)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Veterans Administration Benefits (%)	1.1	3.1	1.1	3.6	0.0	0.0	1.4	0.0	2.6	8.3
Unemployment Compensation (%)	0.5	1.5	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Workmen's Compensation (%)	0.5	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
"Aid to Families with Dependent Children" (AFDC) Assistance (%)	1.6	6.2	1.1	1.8	0.9	0.0	1.4	0.0	0.0	0.0
Public Welfare or Assistance (%)	2.1	1.5	1.7	1.8	1.8	0.0	0.0	5.3	0.0	8.3
Civil Service Benefits (%)	2.7	0.0	3.4	0.0	2.7	0.0	1.4	0.0	0.0	0.0
Union or Employer Disability Benefits (%)	9.6	9.2	5.7	5.5	8.8	10.5	4.3	10.5	2.6	0.0
Union or Employer Retirement or Pension Benefits (%)	5.9	3.1	6.9	9.1	6.2	2.6	8.6	0.0	2.6	0.0
Any Other Benefits	3.2	1.5	3.4	1.8	4.4	0.0	2.9	5.3	5.1	8.3

Table 8-23
Financial Difficulties Experienced by Transplant Recipients at 3, 6, 9, 12, and 15 Months Posttransplant

	Number of Months Posttransplant				
	3 Months	6 Months	9 Months	12 Months	15 Months
Having Difficulty Paying for Immunosuppressive Drugs					
Yes (%)	22.8	22.9	19.3	22.7	23.5
No (%)	77.2	77.1	80.7	77.3	76.5
Receive Assistance in Paying for Drugs					
Yes (%)	97.2	97.0	98.0	98.9	98.0
No (%)	2.8	3.0	2.0	1.1	2.0
Worried About Finances Now					
Extremely Worried (%)	19.8	13.4	15.3	11.2	7.8
Moderately Worried (%)	30.8	28.9	27.3	30.3	41.2
A Little Worried (%)	27.7	39.7	38.0	30.3	29.4
Not At All Worried (%)	21.7	18.1	19.3	28.1	21.6

Fifteen months posttransplant, only 23.5 percent of all patients said that they had difficulty paying for their immunosuppressive drugs, compared with 22.8 percent who reported having difficulty paying for their drugs three months posttransplant. The greatest change was in the percentage of patients who said that they were "extremely worried" about their finances. The percentage of patients who reported being "extremely worried" about their finances decreased from 19.8 percent to 7.8 percent between 3 and 15 months posttransplant.

Tables 8-24 and 8-25 present the financial difficulties experienced by transplant patients at 3, 6, 9, 12, and 15 months posttransplant by initial immunosuppressive protocol and primary renal diagnosis, respectively. At 3 months, 6 months, 9 months, and 15 months posttransplant a slightly higher percentage of patients who initially received CSA + PRED reported having difficulty paying for their immunosuppressive drugs compared with patients who initially received AZA + PRED + ALG. However, it is also interesting to note that, with the exception of three months posttransplant, CSA + PRED patients were less likely to be worried about their finances than were AZA + PRED + ALG patients. As shown in Table 8-24, patients who initially received CSA + PRED were much less likely to report being "extremely worried" or "moderately worried" about their finances and more likely to report being "a little worried" or "not at all worried" than patients who initially received AZA + PRED + ALG.

Table 8-24

Financial Difficulties Experienced by Transplant Recipients at 3, 6, 9, 12 and 15 Months Posttransplant by Initial Immunosuppressive Protocol

	3 Months Posttransplant		6 Months Posttransplant		9 Months Posttransplant		12 Months Posttransplant		15 Months Posttransplant	
	AZA+PRED+ALG	CSA+PRED	AZA+PRED+ALG	CSA+PRED	AZA+PRED+ALG	CSA+PRED	AZA+PRED+ALG	CSA+PRED	AZA+PRED+ALG	CSA+PRED
Having Difficulty Paying for Immunosuppressive Drugs										
Yes (%)	21.3	25.9	19.6	30.9	14.9	26.3	25.0	15.0	18.8	31.6
No (%)	78.7	74.1	80.4	69.1	85.1	71.9	75.0	85.0	81.2	68.4
Receive Assistance Paying for Drugs										
Yes (%)	97.1	97.6	97.7	94.5	96.8	100.0	98.5	100.0	96.9	100.0
No (%)	2.9	2.4	2.3	5.5	3.2	0.0	1.5	0.0	3.1	0.0
Worried About Finances Now										
Extremely Worried (%)	17.5	24.4	14.1	11.8	16.8	12.7	13.7	7.9	9.4	5.3
Moderately Worried (%)	32.7	26.8	31.3	23.2	28.4	25.5	31.4	28.9	46.9	31.6
A Little Worried (%)	28.7	25.6	37.4	44.9	34.7	43.6	27.5	34.2	25.0	36.8
Not at all Worried (%)	21.1	23.2	17.2	20.3	20.0	18.2	27.5	28.9	18.7	26.3

Table 8-25

Financial Difficulties Experienced by Transplant Recipients at 3, 6, 9, 12 and 15 Months Posttransplant by Primary Renal Diagnosis

	3 Months Posttransplant		6 Months Posttransplant		9 Months Posttransplant		12 Months Posttransplant		15 Months Posttransplant	
	Nondiabetes	Diabetes	Nondiabetes	Diabetes	Nondiabetes	Diabetes	Nondiabetes	Diabetes	Nondiabetes	Diabetes
Having Difficulty Paying for Immunosuppressive Drugs										
Yes (%)	23 2	21.5	22.2	25.5	19.6	18.4	22.0	23.7	25.6	16.7
No (%)	76.8	78.5	77.8	74.5	80.4	81.6	78.0	76.3	74.4	83.3
Receive Assistance Paying for Drugs										
Yes (%)	96.8	98.5	96.3	98.5	98.2	97.4	98.0	100.0	97.4	100.0
No (%)	3.2	1.5	3.7	1.5	1.8	2.6	2.0	0.0	2.6	0.0
Worried About Finances Now										
Extremely Worried (%)	17.0	27.7	14.7	9.1	15.2	15.8	11.4	10.5	7.7	8.3
Moderately Worried (%)	31.9	27.7	29.4	27.3	33.0	10.5	30.0	31.6	38.5	50.0
A Little Worried (%)	26.1	32.3	37.3	47.3	33.9	50.0	28.6	36.8	33.3	16.7
Not At All Worried (%)	25.0	12.3	18.6	16.4	17.9	23.7	30.0	21.1	20.5	25.0

With respect to primary renal diagnosis, we found that diabetic patients were more worried about their finances three months following their transplant surgery than were nondiabetic patients. However, as shown in Table 8-25, during the later follow-up periods diabetic patients in the study expressed less concern with their finances. For example, at 15 months posttransplant, only 8.3 percent of diabetic patients said that they were "extremely worried" about their finances, compared with 27.7 percent who said that they were "extremely worried" about their finances three months following transplantation. During the period between 6 and 15 months posttransplant, the two groups were quite similar in their concerns about their financial situation.

Comparisons with Other ESRD Patients

In this section we compare the employment and work disability of participating renal transplant recipients with data from previous studies of end-stage renal disease (ESRD) patients. In particular, we compare the employment and ability to work of patients in the current study with the employment and ability to work of patients from the National Kidney Dialysis and Kidney Transplantation Study (NKDKTS). These data were collected from a sample of 859 end-stage renal disease patients associated with 11 dialysis and transplant centers throughout the United States. Of the 859 patients included in the study, 287 were treated with home hemodialysis, 347 with in-center hemodialysis, 81 with continuous peritoneal dialysis (CPD), and 144 with transplantation. Of the 144 transplant patients, 74 had received a transplant from a living related donor, and 70 from a cadaver.

Many of the measures of employment and work disability used in our current study were also used in the NKDKTS. Not all variables examined in this chapter were included in the NKDKTS (for example, NKDKTS patients were not asked questions concerning the extent to which they worried about their finances or if they had difficulty paying for immunosuppressive drugs). However, information regarding employment status at the time of the survey and the patient's ability to work were collected for NKDKTS patients.

Employment Status--

Table 8-26 compares the employment status of participating transplant recipients 3 months and 15 months posttransplant with ESRD patients from the National Kidney Dialysis and Kidney Transplantation Study. In addition to presenting the employment status of all patients in the current study at 3 and 15 months posttransplant, the employment status of patients is shown separately by primary renal diagnosis (nondiabetes versus diabetes). The employment status of NKDKTS patients at the time they were surveyed is shown for all treatment modalities, as well as for home hemodialysis, in-center hemodialysis, continuous peritoneal dialysis, and transplant patients.

The results of the National Kidney Dialysis and Kidney Transplantation Study (Evans et al., 1987) concluded that although much of the difference in the labor force participation of the various treatment modality groups could be attributed to patient case-mix, transplant patients were significantly more likely to be labor force participants than were in-center hemodialysis patients. As can be seen from Table 8-26, three months following transplant surgery, the percentage of transplant patients from the current study who were employed either full-time or part-time was lower than the corresponding

Table 8-26
Employment Status of Participating Transplant Recipients at 3 and 15 Months Posttransplant Compared with National Kidney Dialysis and Kidney Transplantation Study Patients

	3 Months Posttransplant			15 Months Posttransplant			National Kidney Dialysis and Kidney Transplantation Study				
Employment Status	All Patients	Non-Diabetes	Diabetes	All Patients	Non-Diabetes	Diabetes	All Modalities	Home Hemodialysis	In-Center Hemodialysis	Continuous Peritoneal Dialysis	Transplant
Employed full-time (%)	22.8	23.8	20.0	35.3	41.0	16.7	22.3	26.8	13.0	13.7	40.3
Employed part-time (%)	5.9	7.4	1.5	7.8	7.7	8.3	7.4	9.4	7.5	2.5	5.6
Employed but temporarily laid off (%)	0.8	1.1	0.0	0.0	0.0	0.0	0.6	1.0	0.3	0.0	0.7
Unemployed, looking for work (%)	7.5	9.0	3.1	0.0	0.0	0.0	3.2	2.4	2.9	0.0	6.9
Unemployed, not looking for work (%)	2.4	2.1	3.1	0.0	0.0	0.0	2.9	1.0	3.2	7.5	3.5
Unable to work because of health (%)	34.6	28.0	53.8	23.5	17.9	41.7	39.2	35.9	46.2	47.5	24.3
Homemaker (%)	14.2	14.3	13.8	21.6	17.9	33.3	11.3	12.2	9.8	11.2	13.2
Full-time student (%)	3.1	3.7	1.5	5.9	7.7	0.0	2.5	3.5	0.9	1.2	4.9
Retired (%)	5.9	7.4	1.5	3.9	5.1	0.0	5.0	7.7	16.2	16.2	0.7
Other (%)	2.8	3.2	1.5	2.0	2.6	0.0	0.0	0.0	0.0	0.0	0.0

percentage of transplant patients from the National Kidney Dialysis and Kidney Transplantation Study. Similarly, the percentage of patients who were unable to work because of their health was higher among the patients from the current study, compared with the percentage of NKDKTS transplant patients who were disabled. This, however, is not surprising since three months is probably not an unrealistic period of recuperation for patients following a major surgery such as kidney transplantation. Indeed, by 15 months posttransplant, the employment status of patients from the current study was quite similar to the employment status of NKDKTS transplant patients. Moreover, it is interesting to note that the employment status of nondiabetic patients in the current study quite closely resembles the employment status of transplant patients in the National Kidney Dialysis and Kidney Transplantation Study. The employment status of the diabetic patients in the current study, on the other hand, more closely resembles the employment status of NKDKTS in-center hemodialysis and continuous peritoneal dialysis patients.

In comparing the employment status of transplant patients from the current study with transplant patients from the NKDKTS, it is important to consider the differences in the characteristics of the patients included in the two studies. Such case-mix differences between the patients in the two studies may explain differences in whether or not the patients were employed following transplantation. One major difference between the transplant patients from the two studies is in the length of time between transplantation and when information regarding employment status was collected. Information regarding the employment status of transplant patients in the current study was collected from 3 months to 15 months following surgery, whereas information regarding the employment of transplant patients in the NKDKTS was obtained an average of 4.28 years following transplantation. Indeed, only 19.4 percent of transplant patients in the NKDKTS sample had received their transplants less than one year prior to data collection. In addition, the average age of the transplant patients in the NKDKTS was 37.2 years compared to 42.2 years for patients in the current study. Finally, 26.5 percent of all patients included in the current study are diabetic patients, compared with only 7.9 percent of transplant patients from the National Kidney Dialysis and Kidney Transplantation Study. Thus, differences in the characteristics of the transplant patients included in the two studies (in particular differences in the length of time since transplantation or in the proportion of diabetic patients) may account for the differences in their employment status following transplantation.

Ability to Work--

Table 8-27 compares the ability to work of participating transplant recipients at 3 months and 15 months posttransplant with the ability to work of end-stage renal disease patients from the National Kidney Dialysis and Kidney Transplantation Study. Three months following transplantation, a lower percentage of transplant patients in the current study reported that they were able to work full-time compared with NKDKTS transplant patients. Similarly, compared with transplant patients from the National Kidney Dialysis and Kidney Transplantation Study, a much higher percentage of transplant patients in the current study said that they were not able to work at all three months posttransplant. By 15 months posttransplant, the responses of the two groups were more similar in terms of their ability to work; however,

Table 8-27

Ability to Work of Participating Transplant Recipients at 3 and 15 Months Posttransplant Compared with National Kidney Dialysis and Kidney Transplantation Study Patients

	3 Months Posttransplant			15 Months Posttransplant			National Kidney Dialysis and Kidney Transplantation Study				
Employment Status	All Patients	Non-Diabetes	Diabetes	All Patients	Non-Diabetes	Diabetes	All Modalities	Home Hemodialysis	In-Center Hemodialysis	Continuous Peritoneal Dialysis	Transplant
Able to Work for Pay											
Full-Time (%)	36.9	40.8	26.2	47.1	53.8	25.0	28.2	30.5	16.2	13.6	60.1
Part-Time (%)	17.7	20.1	10.8	19.6	12.8	41.7	21.5	28.8	20.9	11.1	14.0
Not at all (%)	45.4	39.1	63.1	33.3	33.3	33.3	50.3	40.7	62.8	75.3	25.9
Health Prevents Working for Pay											
Yes (%)	53.8	47.9	70.8	33.3	30.8	41.7	60.2	54.7	71.6	74.1	36.4
No (%)	46.2	52.1	29.2	66.7	29.2	58.3	39.8	45.3	28.4	25.9	63.2

NKDKTS transplant patients were still more likely to report being able to work for pay full-time than were patients in the current study. As we observed in the previous section, with respect to their ability to work, nondiabetic patients in the current study more closely resemble NKDKTS transplant patients.

Discussion

In this chapter we examined the labor force participation of renal transplant recipients following their transplant surgery. In addition to asking patients about their employment status at the time they were surveyed, patients were asked a series of questions regarding their ability to work for pay (either full-time or part-time), whether or not they were receiving various disability or retirement benefits, and the extent to which they worried about their personal finances. Patients were also asked whether or not they had difficulty paying for immunosuppressive drugs and the extent to which they received assistance in paying for these medications. Employment status and other work-related variables were collected at several points in time--at 3, 6, 9, 12, and 15 months posttransplant. Information regarding each patient's employment status during the year prior to transplantation was also obtained. Differences in employment and work disability were examined separately for patients in the two initial immunosuppressive protocol groups (AZA + PRED + ALG versus CSA + PRED), and for patients grouped by primary renal diagnosis (diabetes versus nondiabetes).

One advantage frequently mentioned in support of transplantation compared with hemodialysis as a treatment for end-stage renal disease is the potential for allowing patients to return to the labor force. In our analysis we did not observe a dramatic improvement in terms of ability to work; however, with increasing time since transplantation, patients were somewhat more likely to say that they were able to work for pay than they were three months following their transplant surgery. The percentage of patients who said that they were able to work for pay on a full-time basis rose from 36.9 percent at three months posttransplant to 47.1 percent at 15 months posttransplant. Similarly, the percentage of patients who said that they were not able to work at all declined from 45.4 percent to 33.3 percent during the same period of time.

The improvement in transplant patients ability to work was also reflected in their labor force participation following their transplant surgery, although employment levels following transplant surgery did not return to the level of employment reported for the period prior to transplantation. Among the patients included in our study, approximately one-half reported that they were employed (either full-time or part-time) during the year prior to their surgery. Following transplantation the percentage of patients who were employed was much lower. The percentage of transplant recipients who were employed, which was lowest three months following transplant surgery (28.7%), increased slightly over time. However, even 15 months posttransplant, the percentage of patients who were employed either full-time or part-time was lower than the percentage of patients who were employed during the year prior to transplantation.

Employment status--both prior to and following transplantation surgery--was fairly similar for the two initial immunosuppressive protocol groups. Differences in employment status by primary renal diagnosis were much more apparent. Among nondiabetic patients, for example, 40.8 percent said that they were able to work for pay full-time three months following transplant surgery. However, only 26.2 percent of diabetic patients said that they were able to work full-time. Almost two-thirds of diabetic patients indicated that they were not able to work at all, compared with less than 40 percent of nondiabetic patients. Diabetic patients were also much less likely to be employed following transplant surgery. Moreover, the percentage of nondiabetic patients who were employed increased slightly during the period from 3 to 15 months posttransplant. In contrast, the percentage of diabetic patients who were employed remained relatively constant over time.

Thus, the results of our analysis seem to suggest that kidney transplantation is not very effective in allowing previously disabled dialysis patients to return to the labor force. In general, the patients who were employed following their transplant surgery were also employed in the year prior to transplantation. Indeed, the major change in employment status resulted from patients who were employed prior to transplantation moving to the disabled category, although a fairly large number of formerly employed patients entered the retired and the other "unemployed" categories (which includes those unemployed, looking for work). The formerly disabled patients typically remained disabled. Few patients who said that they were disabled prior to transplantation were employed either full-time or part-time following their transplant surgery. Those patients who were retired or who were homemakers prior to transplantation tended to remain in these same categories following transplant surgery.

With a rather large percentage of transplant patients reporting that they are unable to work following transplant surgery, it was not surprising to find that a rather large percentage of participating transplant patients were receiving some form of income support. Social Security Retirement or Disability benefits and Supplemental Security Income (SSI) were the two most commonly cited sources of this support. Consistent with our other finding, diabetic patients were much more likely than nondiabetic patients to be receiving retirement and disability benefits. Interesting, the percentage of patients receiving disability and retirement benefits varied little over time.

Even though a portion of the cost of the treatment of end-stage renal disease is covered under the Medicare End-Stage Renal Disease Program, out-of-pocket costs can impose a significant financial burden on the patient and his or her family. Many patients have private health insurance to help pay for these and other medical expenses; however, others must rely on government programs such as Medicaid to help cover medical expenses. For most patients in our study, finances were a source of major concern at the time of transplant and finances continued to be a source of worry to most patients in the months following their transplant surgery. However, finances appear to become somewhat less of a concern with the passage of time.

In view of recent increases in the costs of immunosuppressive drugs, patients were specifically asked whether or not they had difficulty paying for these medications. In general, less than one-quarter of all patients reported that they had difficulty paying for their immunosuppressive drugs. Moreover, an overwhelming 97.2 percent said that they received assistance in paying for their immunosuppressive drugs (approximately two-thirds of all patients indicated that private insurance helped them pay for these drugs).

CHAPTER 9

THE FUNCTIONAL LIMITATIONS OF KIDNEY TRANSPLANT RECIPIENTS

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Introduction

It is now widely accepted that a medical technology can no longer be judged solely on the basis of its ability to maintain lives. While in the past, the primary concern in evaluating a new technology was its reported efficacy and safety, today concerns have expanded to include other factors, such as the patients' rehabilitation potential. For patients who are debilitated by their condition, an important goal is to restore their ability to function. Consequently, various patient outcomes, such as restored functional ability, have served as indicators of the quality of care patients receive (Bowen, 1987:1578; Brook and Lohr, 1987:3138; Brook et al., 1976; Caper, 1988:49; Donabedian, 1966:166; 1969; 1978; 1980; 1982; 1988:1743; 1988:173; Jelly, 1988:2715; Lohr et al., 1988:5; O'Leary, 1988:1760; Roper and Hackbarth, 1988:91; Starfield, 1974:39).

It is of interest today to make note of the revival of interest in "outcome assessment" as the preferred method by which to assess the quality of patient care (Dubois et al., 1987:1162; 1987:1674; 1988:1624; Ellwood, 1988:1549; Laupacis et al., 1988:1728; Lohr, 1988:37; Luft and Hunt, 1986:2780; Relman, 1988:1220; Roper et al., 1988:1197; Schroeder, 1987:160; 1987:251; Wennberg et al., 1980:277). Undoubtedly, the level of awareness concerning the utility of outcome assessment has been enhanced by the Health Care Financing Administration's decision to publish individual hospital mortality rates (Editorial, 1986:1376; Greenfield et al., 1988:2253; Jencks et al., 1988: 2240; Moses, 1986:2801; Vladeck et al., 1988:122; Wagner et al., 1986:148). Not surprisingly, this decision has been met with sharp criticism as hospitals with high mortality rates argue their case based on the case-mix and disease severity of the patients treated. The primary concern of the future will be the refinement of outcome assessment measures. At this point, the analyses have been too simplistic, overlooking many important factors that are likely to impact upon patient outcomes.

Since end-stage renal disease (ESRD) is a chronic condition, treatment is not viewed as a cure. Therefore, beyond mere survival, evaluation of the therapeutic options for the treatment of kidney disease often includes a consideration of factors such as reduced illness and disability, rehabilitation, and improved quality of life (Gutman et al., 1981:309; Hutchinson et al., 1979:661). However, among chronically ill patients, restoration of function is relative, with significant accomplishment being made when patients are able to function much as they did prior to the onset of their condition.

The term rehabilitation is commonly used to refer to the extent to which a patient is able to return to his or her premorbid level of functioning (i.e., physical rehabilitation) and whether previously employed patients are able to return to work (i.e., vocational rehabilitation). Past studies have shown that end-stage renal disease patients experience some level of functional impairment and a fairly high level of work disability (Evans et al., 1987). However, transplant patients typically have much lower levels of functional impairment than dialysis patients (Hart and Evans, 1987:117s; Evans et al., 1985:553).

Previous chapters of this report have focused on a number of patient outcomes following kidney transplantation, including graft and patient survival (Chapter 6), various clinical outcomes (Chapter 7), and vocational rehabilitation (Chapter 8). In this chapter we turn our attention to physical functioning--another important consideration in assessing the rehabilitation of patients following transplant surgery.

Variables

Functional impairment generally refers to the physical, emotional, and mental limitations in performance experienced by a patient. Several of the instruments commonly used to measure functional impairment focus on the measurement of an individual's ability to participate in activities of daily living. To measure specific functional impairments, we used a series of questions which was taken from the Rand Health Insurance Study (Stewart et al., 1978). Patients were asked 12 questions such as "Does your health limit the kind of vigorous activities you can do, such as running, lifting heavy objects, or participating in strenuous sports?" Patients were asked about limitations in activities at various points in time following surgery, as well as limitations experienced one year prior to transplantation.

To complement the Rand Health Insurance Study questions, an additional set of questions concerning specific functional limitations was incorporated into the survey instrument. These questions, taken from the 1978 Survey of Disability and Work conducted by the Social Security Administration (Bye and Schechter, 1979; 1982), asked if patients were currently limited in their ability to perform other physical functions such as using their fingers to grasp or handle, using their eyes for reading, and lifting and carrying heavy objects.

Finally, all transplant patients were asked to estimate the number of hours per week that they engaged in "light," "medium," and "strenuous" activities during the past month (Stewart et al., 1978; 1981). Examples of light activities included standing or walking slowly, bowling, fishing quietly, playing a musical instrument, and mowing the lawn with a power mower. Medium activities included activities such as bicycling, playing golf, dancing, canoeing (not white water), digging or gardening, doing carpentry, and swimming slowly. Examples of strenuous activities included carrying heavy weights (80 pounds or more), shoveling heavy loads, jogging or running fast, skiing, playing full court basketball, playing handball or squash, and playing touch football.

Results

Patients were asked a series of questions regarding the extent to which they are limited in various physical activities or have specific functional limitations because of their health. Patients were asked about these limitations at several points in time following their transplant surgery--at 3-months, 6-months, 9-months, 12-months, and 15-months posttransplant--as well as one year prior to transplantation. Differences in functional limitations are examined separately for patients in the two initial immunosuppressive protocol groups (AZA + PRED + ALG versus CSA + PRED), as well as for patients grouped by primary renal diagnosis (diabetes versus nondiabetes). The longitudinal nature of the study design provides an opportunity to examine changes in the physical limitations experienced by transplant recipients over time. In addition, whenever possible the functional limitations experienced by participating transplant recipients are compared with other kidney dialysis and transplant patients.

Our discussion of results is divided into three sections. In the first section we examine differences in the functional limitations of transplant patients by initial immunosuppressive protocol, as well as by primary renal diagnosis. In this section we compare the limitations of transplant patients three months posttransplant with the limitations experienced one year prior to transplantation. In the second section we examine differences in the physical limitations at three-month intervals from 3 to 15 months posttransplant. The final section presents a comparison of the limitations experienced by participating transplant recipients with other kidney dialysis and transplant patients who participated in the National Kidney Dialysis and Kidney Transplantation Study.

Differences by Initial Immunosuppressive Protocol and Primary Renal Diagnosis

In this section we examine several measures of functional ability: (1) limitations of daily activity; (2) other physical limitations; and (3) levels of physical activity. The analysis presented here is largely descriptive in nature. With the exception of initial immunosuppressive protocol and primary renal diagnosis, we do not consider other case-mix variables in examining the functional limitations of renal transplant recipients following transplant surgery.

Limitations of Daily Activity--

As described earlier, all participating renal transplant patients were asked an extensive battery of questions pertaining to their level of functioning following the transplant surgery. For example, patients were asked if they have trouble bending, lifting, or stooping because of their health or if they have to stay indoors most or all of the day because of their health. In addition to asking patients if they are limited in particular activities three months posttransplant, patients were also asked if they experienced these same physical limitations one year prior to their transplant surgery.

Table 9-1 compares the limitations experienced by transplant recipients 3 months following surgery with the limitations reported one year prior to transplantation. Clearly, prior to transplant surgery, patients experienced considerable physical limitations. More than 50 percent reported that they were limited in the kind of vigorous activities (i.e., running, lifting heavy objects, participating in strenuous sports) they could do; had trouble walking several blocks or climbing a few flights of stairs; were unable to do certain kinds or amounts of work, housework, or schoolwork; were kept from working at a job, doing work around the house, or going to school; or were limited in some way from doing something they wanted to do. On the other hand, fewer than 20 percent said that they needed help eating, dressing, bathing, or using the toilet or that they needed help in walking (for example, another person, cane, crutches, etc.) one year prior to their transplant surgery.

In contrast, patients reported considerably fewer physical limitations three months posttransplant. Three months following their surgery almost three-quarters (74.8%) of the transplant patients reported that they are limited in the kind of vigorous activities that they can do, such as running, lifting heavy objects, and participating in strenuous sports. Also over 60 percent said that they are limited in some way from doing something that they want to do. However, far fewer reported that they have trouble walking several blocks or climbing a few flights of stairs; are unable to do certain kinds or amounts of work, housework, or schoolwork; or are kept from working at a job, doing work around the house, or going to school three months after receiving their kidney transplant. Also, three months following surgery, fewer patients indicated that they have trouble walking one

Table 9-1
Limitations Experienced by Participating Transplant Recipients
One Year Prior to Transplant Surgery and Three Months Posttransplant

	Year Prior to Transplant	3 Months Posttransplant
BECAUSE OF HEALTH DID PATIENT:		
Need assistance traveling around community (%)	23.9	20.9
Stay indoors most or all of the day because of health (%)	22.1	14.2
Stay in bed most or all of the day because of health (%)	23.9	11.4
Limited in vigorous activities (%)	78.3	74.8
Trouble walking several blocks or climbing stairs because of health (%)	68.8	43.7
Trouble bending, stooping, or lifting because of health (%)	44.9	42.1
Trouble walking one block or climbing one flight of stairs because of health (%)	46.0	27.6
Help in walking such as another person, cane, crutches, etc. (%)	15.8	13.0
Unable to do certain amounts of work, housework, or schoolwork (%)	63.2	48.0
Unable to work at job or do work around house (%)	58.1	43.3
Need help eating, dressing, bathing, or using toilet (%)	5.5	5.1
Limited in any way from doing anything he wants to (%)	77.2	62.2

block or climbing one flight of stairs because of their health or that they stay in bed most or all of the day because of health compared with one year prior to surgery.

The physical limitations reported by patients in the two initial immunosuppressive protocol groups one year prior to surgery and three months posttransplant are shown in Table 9-2. Three months after transplant surgery, the two initial immunosuppressive protocol groups do not differ greatly in terms of functional limitations. .One year prior to transplant surgery, however, the patients in the AZA + PRED + ALG group were much more limited in their physical functioning than were patients in the CSA + PRED group. For example, one year prior to surgery 28.3 percent of the patients in the AZA + PRED + ALG group said they needed assistance in traveling around their community because of their health, while only 14.9 percent of the CSA + PRED patients said that they needed such assistance. As can be seen in Table 9-2, three months after surgery the patients in the AZA + PRED + ALG group report a dramatic improvement in their physical functioning compared with one year prior to transplantation. CSA + PRED patients, on the other hand, report much less change in terms of their functional ability. CSA + PRED patients report an improvement for some of the activities, such as the percentage of patients who stay in bed most of all of the day because of their health, and the percentage who have trouble walking one block or climbing one flight of stairs because of their health. However, for other activities such as the percentage who said they must stay indoors most or all of the day because of their health, and the percentage who need assistance in traveling around the community, there is little change following transplantation.

Table 9-2
Limitations Experienced by Participating Transplant Recipients One Year Prior to Transplant Surgery and Three Months Posttransplant by Initial Immunosuppressive Protocol

	Year Prior to Transplant		3 Months Posttransplant	
	AZA+PRED+ALG	CSA+PRED	AZA+PRED+ALG	CSA+PRED
BECAUSE OF HEALTH DID PATIENT:				
Need assistance traveling around community (%)	28.3	14.9	22.9	16.9
Stay indoors most or all of the day because of health (%)	25.9	13.8	14.6	13.3
Stay in bed most or all of the day because of health (%)	26.5	18.4	12.9	8.4
Limited in vigorous activities (%)	81.1	72.4	71.9	80.7
Trouble walking several blocks or climbing stairs because of health (%)	73.5	58.6	43.3	44.6
Trouble bending, stooping, or lifting because of health (%)	47.0	40.2	40.9	44.6
Trouble walking one block or climbing one flight of stairs because of health (%)	48.6	40.2	26.3	30.1
Help in walking such as another person, cane, crutches, etc. (%)	17.8	11.5	14.0	10.8
Unable to do certain amounts of work, housework, or schoolwork (%)	66.5	56.3	48.0	48.2
Unable to work at job or do work around house (%)	61.6	40.6	43.9	42.2
Need help eating, dressing, bathing, or using toilet (%)	6.5	3.4	6.4	2.4
Limited in any way from doing anything he wants to (%)	81.6	67.8	60.8	65.1

Table 9-3 compares the physical limitations reported by transplant patients one year prior to surgery and three months posttransplant by primary renal diagnosis. Both one year prior to transplantation and three months posttransplant, diabetic patients report higher levels of impairment than nondiabetic patients. For example, one year prior to transplant surgery, 26.1 percent of diabetic patients said that they had to stay indoors most or all of the day because of their health, compared with only 20.7 percent of nondiabetic patients. Similarly, three months posttransplant, the percentage of patients who said that they had to stay indoors most or all of the time because of their health was 20.0 percent for diabetic patients and 12.2 for nondiabetic patients.

As can be seen in Table 9-3, both groups generally report fewer limitations three months following surgery. However, the improvement in physical functioning following transplantation is most obvious among nondiabetic patients. Nondiabetic patients consistently reported lower levels of functional impairment three months following surgery than they reported one year prior to transplantation for each of the 12 limitations listed in Table 9-3. Diabetic patients reported dramatic improvements for many of the limitations. Following transplantation fewer diabetic patients said that they had to stay in bed most or all of the day because of their health or that they had trouble walking or climbing stairs because of their health, compared with one year prior to their surgery. However, with respect to other limitations diabetic patients reported little or no change in their functional ability. For 3 of the 12 limitations listed in Table 9-3, the percentage of diabetic patients who reported that they were limited in the activity--those needing assistance traveling around their community, those needing help

Table 9-3
Limitations Experienced by Participating Transplant Recipients One Year Prior to Transplant Surgery and Three Months Posttransplant by Primary Renal Diagnosis

	Year Prior to Transplant		3 Months Posttransplant	
	Nondiabetes	Diabetes	Nondiabetes	Diabetes
BECAUSE OF HEALTH DID PATIENT:				
Need assistance traveling around community (%)	18.8	39.1	10.6	50.8
Stay indoors most or all of the day because of health (%)	20.7	26.1	12.2	20.0
Stay in bed most or all of the day because of health (%)	21.2	31.9	9.5	16.9
Limited in vigorous activities (%)	76.4	84.1	75.1	73.8
Trouble walking several blocks or climbing stairs because of health (%)	68.0	71.0	39.7	55.4
Trouble bending, stooping, or lifting because of health (%)	43.3	49.3	39.7	49.2
Trouble walking one block or climbing one flight of stairs because of health (%)	43.8	52.2	21.7	44.6
Help in walking such as another person, cane, crutches, etc. (%)	12.3	26.1	6.9	30.8
Unable to do certain amounts of work, housework, or schoolwork (%)	61.1	69.6	45.0	56.9
Unable to work at job or do work around house (%)	55.2	66.7	37.0	61.5
Need help eating, dressing, bathing, or using toilet (%)	4.4	8.7	3.2	10.8
Limited in any way from doing anything he wants to (%)	76.4	79.7	58.7	72.3

in walking, and those needing help eating, dressing, bathing or using the toilet--actually increased following transplantation.

The results of this analysis indicate that diabetic patients are much more likely to be functionally impaired than nondiabetic patients--both prior to their transplant surgery, as well as three months posttransplant. While, in general, both groups are less impaired three months posttransplant when compared with one year prior to transplantation, the improvement is greatest among the nondiabetic patient group. As a result, the differences in the reported levels of functional impairment between the two groups generally widen in the first three months following transplant surgery.

Other Physical Limitations--

In addition to the limitations examined above, patients were asked whether or not their health limited their ability to perform other physical functions. These questions, taken from the 1978 Survey of Disability and Work (Bye and Schechter, 1982), asked if patients were currently limited in their ability to perform other physical functions such as using their fingers to grasp or handle, using their eyes for reading, and lifting and carrying heavy objects. As shown in Table 9-4, three months following surgery, 11.8 percent of all patients reported being limited in their ability to reach and 10.2 percent reported being limited in their ability to use their fingers to grasp or handle. Over one-fourth of all patients said they are limited in terms of their vision--25.2 percent indicated that they have difficulty using their eyes for inspection of things and 29.1 percent said that they are limited in their ability to use their eyes for reading. Finally, most patients said they have trouble lifting or carrying heavy weights. While only 22.4 percent

Table 9-4
Percent of Participating Transplant Recipients With Various Functional Limitations Three Months Following Transplant Surgery by Initial Immunosuppressive Protocol and Primary Renal Diagnosis

	All Patients	Primary Renal Diagnosis		Initial Immunosuppressive Protocol	
		Nondiabetes	Diabetes	AZA + PRED + ALG	CSA + PRED
Reach (%)	11.8	12.7	9.2	12.9	9.6
Use Fingers to Grasp or Handle (%)	10.2	10.1	10.8	9.4	12.0
Use Eyes For Inspection of Things (%)	25.2	14.3	56.9	27.5	20.5
Use Eyes For Reading (%)	29.1	19.0	58.4	31.0	25.3
Lift or Carry Weights Up to 10 Pounds (%)	22.4	20.6	27.7	21.1	25.3
Lift or Carry Weights Up to 25 Pounds (%)	56.3	55.6	58.5	55.0	59.0
Lift or Carry Weights Up to 50 Pounds (%)	78.7	77.8	81.5	76.6	83.1

indicated that they have trouble lifting or carrying up to 10 pounds, a much higher percentage of patients have difficulty lifting or carrying up to 25 pounds (56.3%) and an even higher percentage of patients have difficulty lifting or carrying up to 50 pounds (78.7%) three months posttransplant.

Table 9-4 also shows the percentages of transplant recipients with these various limitations by primary renal diagnosis and initial immunosuppressive protocol. With respect to primary renal diagnosis, the most obvious difference between the two groups involves limitations associated with transplant patient's use of their eyes. Perhaps not surprisingly, diabetic patients report much more difficulty with their vision than nondiabetic patients. For example, three months following transplant surgery, 56.9 percent of diabetic patients reported that their health limited their ability to use their eyes for inspection of things and 58.4 percent said their health limited their ability to use their eyes for reading, compared with 14.3 percent of nondiabetic patients who said they had difficulty using their eyes for inspection of things and 19.0 percent of nondiabetic patients who said they had difficulty using their eyes for reading. Diabetic and nondiabetic patients did not differ, however, in their ability to reach, to use their fingers to grasp or handle, or to lift and carry heavy weights. Likewise, little difference was observed in the limitations experienced by transplant patients based on their initial immunosuppressive drug protocol.

Levels of Physical Activity--

Finally, three months following transplantation, patients were asked to estimate the number of hours per week that they engaged in "light," "medium," and "strenuous" activities during the past month (Stewart et al., 1981). Table 9-5 summarizes the transplant patients' level of activity three months posttransplant, overall as well as by initial immunosuppressive protocol and primary renal diagnosis. Almost three-quarters (71.8%) of patients reported that they spent six or more hours a week performing "light" activities such as standing or walking slowly, bowling, fishing quietly, playing musical instruments, or mowing the lawn with a power mower. Similarly, 31.1 percent of the patients indicated that they spent six or more hours a week engaged in "medium" activities like bicycling, playing golf, dancing, canoeing (not white water), digging or gardening, doing carpentry, and swimming. However, only 5.2 percent said that they spent six or more hours each week participating in "strenuous" physical activity, including carrying heavy weights (80 pounds or more), shoveling heavy loads, jogging or running fast, skiing, playing full court basketball, playing handball or squash, and playing touch football. Of all participating transplant recipients, only 8.0 percent said they performed no light activities and 35.1 percent said they did not participate in medium physical activity. However, most patients (83.7%) perform no strenuous physical activities. In summary, most transplant recipients engage in light and medium activities, while only a small percentage participate in strenuous physical activity on a regular basis.

As can be seen in Table 9-5, nondiabetic patients are more likely than diabetic patients to be physically active three months following transplant surgery. For example, 95.4 percent of diabetic patients report that they spend no time in strenuous physical activity, compared with 79.6 percent of nondiabetic patients. The percentage of diabetic patients who report no medium physical activity (47.7%) is also higher than the percentage among

Table 9-5
Levels of Physical Activity of Participating Transplant Recipients Three Months Posttransplant by Initial Immunosuppressive Protocol and Primary Renal Diagnosis

	All Patients	Primary Renal Diagnosis		Initial Immunosuppressive Protocol	
		Nondiabetes	Diabetes	AZA + PRED + ALG	CSA + PRED
Light Activities					
0 Hours (%)	8.0	5.9	13.8	9.5	4.9
1-5 Hours (%)	20.3	21.0	18.5	15.4	30.5
6-15 Hours (%)	23.5	17.7	40.0	24.3	22.0
16-25 Hours (%)	23.9	26.3	16.9	25.4	20.7
26-35 Hours (%)	12.0	14.5	4.6	11.2	13.4
36 or More Hours (%)	12.4	14.5	6.2	14.2	8.5
Medium Activities					
0 Hours (%)	35.1	30.6	47.7	32.5	40.2
1 Hour (%)	12.7	11.3	16.9	13.6	11.0
2-5 Hours (%)	21.1	22.0	18.5	21.9	19.5
6-10 Hours (%)	18.7	21.5	10.8	16.6	23.2
11-15 Hours (%)	5.2	6.5	1.5	5.3	4.9
16 or More Hours (%)	7.2	8.1	4.6	10.1	1.2
Strenuous Activities					
0 Hours (%)	83.7	79.6	95.4	80.5	90.2
1 Hour (%)	3.6	4.8	0.0	4.7	1.2
2-5 Hours (%)	7.6	9.1	3.1	8.9	4.9
6-10 Hours (%)	3.6	4.8	0.0	4.1	2.4
11-15 Hours (%)	0.8	1.1	0.0	0.6	1.2
16 or More Hours (%)	0.8	0.5	1.5	1.2	0.0

nondiabetic patients (30.6%). Finally, 13.8 percent of diabetic patients say that they perform no light activities, compared with only 5.9 percent of nondiabetic patients. Differences in the level of physical activity of patients based on initial immunosuppressive protocol are less obvious. However, based on the amount of medium and strenuous activities performed, the AZA + PRED + ALG patient group appears to be slightly more active than the CSA + PRED patient group.

Changes in Functional Limitations Over Time

The data presented thus far have shown an improvement in the level of physical functioning of renal transplant recipients three months following surgery, when compared with physical functioning one year prior to transplantation. In this section, we address the question of whether or not the patients' physical functioning continues to improve in the months following transplantation. The Baseline Patient Questionnaire was used to obtain information concerning physical functioning one year prior to transplantation and three months posttransplant. In addition, Follow-up Patient Questionnaires were used to assess transplant patients' functional ability at 6, 9, 12, and 15 months posttransplant. Thus, we are able to examine the extent to which functional limitations experienced by transplant recipients change over time.

Limitations of Daily Activity--

In the previous section of this chapter, we observed an improvement in the functional ability of renal transplant patients in the first three months following their surgery. While, in general, all patient groups reported fewer physical limitations following surgery than they did prior to their surgery, the improvements in physical functioning were greater among nondiabetic than among diabetic patients. In this section we focus on further changes in the functional ability of transplant patients by examining the limitations reported by patients at three-month intervals following surgery.

Table 9-6 presents the limitations experienced by patients at 3, 6, 9, 12, and 15 months posttransplant. The table also shows the limitations reported by patients one year prior to transplantation. Earlier we observed that the general functional ability of renal transplant patients improves dramatically during the first three months posttransplant. And, as can be seen in Table 9-6, the functional ability of transplant patients continues to improve during the first 12 months following their transplant surgery. In the case of a few activities (i.e., those limited in vigorous activities, those needing assistance walking), there is little change in pretransplant and posttransplant levels of impairment. However, dramatic improvements in functional ability are observed for most of the activities listed in Table 9-6. For example, one year prior to transplantation, 46.0 percent of patients reported that they had trouble walking one block or climbing one flight of stairs because of their health and 68.8 percent of patients reported that they had trouble walking several blocks or climbing a few flights of stairs because of their health. One year following their surgery, only 16.9 percent of patient still had difficulty walking one block or climbing a single flight of stairs and 33.7 percent of patients said they had difficulty walking several blocks or climbing a few flights of stairs because of their health. Similarly, 23.9 percent of all patients said that they needed assistance traveling around their community because of their health and 22.1 percent said that they had

Table 9-6

Limitations Experienced by Participating Renal Transplant Recipients One Year Prior to Transplant and at 3, 6, 9, 12, and 15 Months Posttransplant

	Prior to Transplant	Months Posttransplant				
		3 Months	6 Months	9 Months	12 Months	15 Months
BECAUSE OF HEALTH DID PATIENT:						
Need assistance traveling around community (%)	23.9	20.9	18.1	12.5	10.1	11.5
Stay indoors most or all of the day because of health (%)	22.1	14.2	12.1	7.9	4.5	5.8
Stay in bed most or all of the day because of health (%)	23.9	11.4	9.9	6.9	5.6	3.8
Limited in vigorous activities (%)	78.3	74.8	74.1	81.6	73.0	80.4
Trouble walking several blocks or climbing stairs because of health (%)	68.8	43.7	40.9	38.8	33.7	40.4
Trouble bending, stooping, or lifting because of health (%)	44.9	42.1	35.8	37.5	31.5	32.7
Trouble walking one block or climbing one flight of stairs because of health (%)	46.0	27.6	21.6	20.4	16.9	19.2
Help in walking such as another person, cane, crutches, etc. (%)	15.8	13.0	12.1	13.2	13.5	13.5
Unable to do certain amounts of work, housework, or schoolwork (%)	63.2	48.0	46.1	50.0	44.9	48.1
Unable to work at job or do work around house (%)	58.1	43.3	35.8	36.2	30.3	40.4
Need help eating, dressing, bathing, or using toilet (%)	5.5	5.1	2.8	3.3	2.2	0.0
Limited in any way from doing anything he wants to (%)	77.2	62.2	57.3	55.9	50.6	51.9

to stay indoors most or all of the day because of their health one year prior to transplantation. One year after their transplant surgery, however, only 10.1 percent said they needed assistance traveling around their community and only 4.5 percent said that they had to stay indoors most or all of the day because of their health. The data contained in Table 9-6 also suggest that beyond one year posttransplant, further improvement in physical functioning may not occur. However, this may simply reflect the smaller number of patients for whom 15-month follow-up data were available.

While our earlier analysis indicated that renal transplant recipients experience fewer limitations three months following transplantation compared with limitations reported one year prior to transplantation, it also appears that the improvements in functional ability are greater for some patient groups than for others. Tables 9-7 and 9-8 present comparisons of the limitations experienced by participating transplant recipients 3, 6, 9, 12, and 15 months posttransplant by initial immunosuppressive protocol and primary renal diagnosis, respectively. As can be seen in Table 9-7, in general the functional ability of both initial immunosuppressive protocol groups continues to improve during the period from 3 to 12 months following surgery. During each of the follow-up periods, the AZA + PRED + ALG patients report slightly higher levels of impairment than CSA + PRED patients, although this difference is not great. However, it should also be recognized that the AZA + PRED + ALG patients were more limited in their physical functioning than were CSA + PRED patients prior to their transplant surgery (Table 9-2).

Table 9-7
Limitations Experienced by Participating Transplant Recipients 3, 6, 9, 12, and 15 Months Posttransplant by Initial Immunosuppression Protocol

	3 Months Posttransplant		6 Months Posttransplant		9 Months Posttransplant		12 Months Posttransplant		15 Months Posttransplant	
	AZA•PRED•ALG	CSA•PRED	AZA•PRED•ALG	CSA•PRED	AZA•PRED•ALG	CSA•PRED	AZA•PRED•ALG	CSA•PRED	AZA•PRED•ALG	CSA•PRED
BECAUSE OF HEALTH DID PATIENT:										
Need assistance traveling around community (%)	22.9	16.9	19.6	14.5	14.7	8.8	11.8	7.9	15.2	5.3
Stay indoors most or all of the day because of health (%)	14.6	13.3	14.7	5.8	8.4	7.0	5.9	2.6	9.1	0.0
Stay in bed most or all of the day because of health (%)	12.9	8.4	11.7	5.8	6.3	5.3	5.9	5.3	6.1	0.0
Limited in vigorous activities (%)	71.9	80.7	73.6	75.4	82.1	80.7	72.5	73.7	78.8	78.9
Trouble walking several blocks or climbing stairs because of health (%)	43.3	44.6	42.9	36.2	41.1	35.1	35.3	31.6	42.4	36.8
Trouble bending, stooping, or lifting because of health (%)	40.9	44.6	36.2	34.8	37.9	36.8	35.3	26.3	39.4	21.1
Trouble walking one block or climbing one flight of stairs because of health (%)	26.3	30.1	22.1	20.3	22.1	17.5	21.6	10.5	24.2	10.5
Help in walking such as another person, cane, crutches, etc. (%)	14.0	10.8	13.5	8.7	13.7	12.3	15.7	10.5	15.2	10.5
Unable to do certain amounts of work, housework, or schoolwork (%)	48.0	48.2	46.6	44.9	51.6	47.4	41.2	50.0	54.5	36.8
Unable to work at job or do work around house (%)	43.9	42.2	36.8	33.3	41.1	28.1	37.3	21.1	42.4	36.8
Need help eating, dressing, bathing, or using toilet (%)	6.4	2.4	3.7	0.0	3.2	3.5	3.9	0.0	0.0	0.0
Limited in any way from doing anything he wants to (%)	60.8	65.1	57.7	56.5	56.8	54.4	47.1	55.3	60.6	36.8

Table 9-8
Limitations Experienced by Participating Transplant Recipients 3, 6, 9, and
15 Months Posttransplant by Primary Renal Diagnosis

	3 Months Posttransplant		6 Months Posttransplant		9 Months Posttransplant		12 Months Posttransplant		15 Months Posttransplant	
	Nondiabetes	Diabetes	Nondiabetes	Diabetes	Nondiabetes	Diabetes	Nondiabetes	Diabetes	Nondiabetes	Diabetes
BECAUSE OF HEALTH DID PATIENT:										
Need assistance traveling around community (%)	10.6	50.8	9.8	45.5	8.1	31.6	5.7	26.3	2.5	41.7
Stay indoors most or all of the day because of health (%)	12.2	20.0	6.8	29.1	5.3	15.8	5.7	0.0	5.0	8.3
Stay in bed most or all of the day because of health (%)	9.5	16.9	6.8	20.0	5.3	7.9	7.1	0.0	5.0	0.0
Limited in vigorous activities (%)	75.1	73.8	70.8	85.5	78.9	89.5	68.6	89.5	75.0	91.7
Trouble walking several blocks or climbing stairs because of health (%)	39.7	55.4	38.2	58.4	35.1	50.0	32.9	36.8	37.5	50.0
Trouble bending, stooping, or lifting because of health (%)	39.7	49.2	33.9	41.8	36.0	42.1	31.4	31.6	32.5	33.3
Trouble walking one block or climbing one flight of stairs because of health (%)	21.7	44.6	17.5	34.5	16.7	31.6	14.3	26.3	17.5	25.0
Help in walking such as another person, cane, crutches, etc. (%)	6.9	30.8	5.8	32.7	8.1	34.2	7.1	36.8	5.0	41.7
Unable to do certain amounts of work, housework, or schoolwork (%)	45.0	56.9	41.8	60.0	48.2	55.3	41.4	57.9	45.0	58.3
Unable to work at job or do work around house (%)	37.0	61.5	29.9	54.5	28.9	57.9	25.7	47.4	37.5	50.0
Need help eating, dressing, bathing, or using toilet (%)	3.2	10.8	2.3	3.6	3.5	2.6	1.4	5.3	0.0	0.0
Limited in any way from doing anything he wants to (%)	58.7	72.3	52.5	72.7	47.4	81.6	45.7	68.4	50.0	58.3

In our previous analysis we observed that both diabetic and nondiabetic patients are less impaired three months posttransplant than they were prior to their transplant surgery. In addition, we observed the improvement during the first three months posttransplant to be greatest among the nondiabetic patient group. As shown in Table 9-8, the functional ability of both groups continues to improve over time. However, perhaps because of their higher initial level of functional impairment, the improvement in functional ability from 3-12 months posttransplant is most dramatic in the case of the diabetic patient group. These data suggest that among nondiabetic patients, much of the improvement in physical functioning occurs in the first three months posttransplant, whereas among diabetic patients the improvement is not apparent until 9-12 months posttransplant. In summary, even after transplantation, diabetic patients are more functionally impaired than nondiabetic patients. However, it is also important to note that the level of physical functioning of both groups is greatly improved over their level of functioning one year prior to transplantation.

Other Physical Limitations--

Table 9-9 presents a comparison of the ability of transplant patients to perform other physical functions such as using their fingers to grasp or handle, using their eyes for reading, and lifting and carrying heavy objects at three months intervals following transplant surgery. As the table clearly shows, over time transplant patients generally improve with respect to their ability to reach, to use their fingers to grasp or handle, and to lift or carry heavy weights. However, as a consequence of steroid use, patients become

Table 9-9
Percent of Transplant Recipients With Various Functional Limitations
3, 6, 9, 12, and 15 Months Posttransplant

	Months Posttransplant				
	3 Months	6 Months	9 Months	12 Months	15 Months
Reach (%)	11.8	9.1	9.2	9.0	5.8
Use fingers to grasp or handle (%)	10.2	8.2	12.5	5.6	3.8
Use eyes for inspection of things (%)	25.2	28.4	28.3	25.8	42.3
Use eyes for reading (%)	29.1	25.9	25.7	30.3	40.4
Lift or cary weights up to 10 pounds (%)	22.4	12.9	14.5	18.0	11.5
Lift or carry weights up to 25 pounds (%)	56.3	37.9	41.4	44.9	40.4
Lift or carry weights up to 50 pounds (%)	78.7	70.7	71.7	66.3	65.4

even more limited in their ability to use their eyes for reading or inspection of things.

Table 9-10 compares the functional limitations of transplant patients at 3, 6, 9, 12, and 15 months posttransplant by initial immunosuppressive protocol. Table 9-11 presents a similar comparison for patients grouped by primary renal diagnosis. In general, patients in both initial immunosuppressive protocol groups improve over time in terms of functional ability, with the exception of their ability to use their eyes for reading or for inspection of things. Both groups report increased problems with their vision, although the problem appears to be greater among AZA + PRED + ALG patients than among CSA + PRED patients. It should also be noted that a higher percentage of AZA + PRED + ALG patients consistently report problems with their vision than is true for CSA + PRED patients. This, however, may reflect the fact that the AZA + PRED + ALG patient group has a higher percentage of diabetic patients than the CSA + PRED patient group.

As can be seen in Table 9-11, the major difference in the limitations experienced by diabetic and nondiabetic patients is in their ability to use their eyes. As noted in our earlier analysis, three months following transplantation, diabetic patients report far more difficulty using their eyes than nondiabetic patients. It is, however, interesting to note that the vision problems experienced by diabetic patients do not appear to increase with time. Nondiabetic patients, on the other hand, report increased vision problems during their first 15 months posttransplant.

Table 9-10
Percent of Transplant Recipients With Various Functional Limitations, 3, 6, 9, 12, and
15 Months Posttransplant by Initial Immunosuppressive Protocol

	3 Months Posttransplant		6 Months Posttransplant		9 Months Posttransplant		12 Months Posttransplant		15 Months Posttransplant	
	AZA+PRED+ALG	CSA+PRED	AZA+PRED+ALG	CSA+PRED	AZA+PRED+ALG	CSA+PRED	AZA+PRED+ALG	CSA+PRED	AZA+PRED+ALG	CSA+PRED
Reach (%)	12.9	9.6	6.7	14.5	7.4	12.3	9.8	7.9	9.1	0.0
Use Fingers to Grasp or Handle (%)	9.4	12.0	10.4	2.9	10.5	15.8	3.9	7.9	6.1	0.0
Use Eyes for Inspection of Things (%)	27.5	20.5	30.1	24.6	31.6	22.8	27.5	23.7	48.5	31.6
Use Eyes For Reading (%)	31.0	25.3	26.4	24.6	28.4	21.1	29.4	31.6	42.4	36.8
Lift or Carry Weights Up to 10 Pounds (%)	21.1	25.3	10.4	18.8	14.7	14.0	23.5	10.5	12.1	10.5
Lift or Carry Weights Up to 25 Pounds (%)	55.0	59.0	37.4	39.1	42.1	40.4	47.1	42.1	42.4	36.8
Lift or Carry Weights Up to 50 Pounds (%)	76.6	83.1	69.3	73.9	74.7	66.7	68.6	63.2	66.7	63.2

Table 9-11
Percent of Transplant Recipients With Various Functional Limitations 3, 6, 9, 12, and 15 Months Posttransplant by Primary Renal Diagnosis

	3 Months Posttransplant		6 Months Posttransplant		9 Months Posttransplant		12 Months Posttransplant		15-Months Posttransplant	
	Nondiabetes	Diabetes	Nondiabetes	Diabetes	Nondiabetes	Diabetes	Nondiabetes	Diabetes	Nondiabetes	Diabetes
Reach (%)	12.7	9.2	10.2	5.5	10.5	5.3	8.6	10.5	5.0	8.3
Use Fingers to Grasp or Handle (%)	10.1	10.8	7.9	9.1	12.3	13.2	4.3	10.5	5.0	0.0
Use Eyes for Inspection of Things (%)	14.3	56.9	19.2	58.2	19.3	55.3	18.6	52.6	37.5	58.3
Use Eyes For Reading (%)	19.0	58.4	16.9	54.5	17.5	50.0	27.1	42.1	40.0	41.7
Lift or Carry Weights Up to 10 Pounds (%)	20.6	27.7	11.9	16.4	14.9	13.2	20.0	10.5	12.5	8.3
Lift or Carry Weights Up to 25 Pounds (%)	55.6	58.5	37.9	38.2	42.1	39.5	42.9	52.6	45.0	25.0
Lift or Carry Weights Up to 50 Pounds (%)	77.8	81.5	70.1	72.7	71.9	71.1	62.9	78.9	67.5	58.3

Levels of Physical Activity--

As noted earlier, three months following transplant surgery, most transplant recipients engage in light and medium activities, while only a small percentage participate in strenuous physical activity on a regular basis. Major differences in the level of physical activity of patients based on initial immunosuppressive protocol are not apparent; however, the AZA + PRED + ALG patient group was slightly more likely than the CSA + PRED patient group to engage in medium and strenuous activities. Nondiabetic patients, on the other hand, are more likely than diabetic patients to be physically active three months following transplant surgery.

Tables 9-12 and 9-13 compare the levels of physical limitations reported by transplant patients 3, 6, 9, 12, and 15 months following transplant surgery by initial immunosuppressive protocol and primary renal diagnosis, respectively. As can be seen in Table 9-12, the percentage of patients who report that they spend no time each week engaged in light, medium, and strenuous activities decreases with time since transplantation. This is true for patients who initially received AZA + PRED + ALG, as well as for patients in the CSA + PRED initial immunosuppressive protocol group. Moreover, with the passage of time since their transplant surgery, both diabetics and nondiabetics spend more time engaged in various physical activities (Table 9-13). Nondiabetic patients, however, continue to be more active physically than diabetic patients.

Comparisons with Other ESRD Patients

In this section we compare the functional limitations experienced by participating renal transplant recipients with data from previous studies of

Table 9-12
Levels of Physical Activity of Participating Transplant Recipients 3, 6, 9, 12, and 15 Months Posttransplant by Initial Immunosuppressive Protocol

	3 Months Posttransplant		6 Months Posttransplant		9 Months Posttransplant		12 Months Posttransplant		15-Months Posttransplant	
	AZA•PRED•ALG	CSA•PRED	AZA•PRED•ALG	CSA•PRED	AZA•PRED•ALG	CSA•PRED	AZA•PRED•ALG	CSA•PRED	AZA•PRED•ALG	CSA•PRED
Light Activities										
0 Hours (%)	9.5	4.9	8.6	2.9	9.5	3.5	16.0	5.3	3.1	5.3
1-5 Hours (%)	15.4	30.5	17.2	20.3	20.0	22.8	16.0	23.7	18.8	26.3
6-15 Hours (%)	24.3	22.0	25.8	29.0	25.3	26.3	26.0	21.1	25.0	31.6
16-25 Hours (%)	25.4	20.7	20.2	18.8	21.1	24.6	12.0	18.4	15.6	10.5
26-35 Hours (%)	11.2	13.4	7.4	8.7	10.5	8.8	12.0	13.2	15.6	15.8
36 or More Hours (%)	14.2	8.5	20.9	20.3	13.7	14.0	18.0	18.4	21.9	10.5
Medium Activities										
0 Hours (%)	32.5	40.2	28.8	32.4	33.7	33.3	31.4	21.1	21.9	31.6
1 Hour (%)	13.6	11.0	8.6	5.9	11.6	1.8	7.8	5.3	9.4	5.3
2-5 Hours (%)	21.9	19.5	24.5	35.3	23.2	29.8	21.6	36.8	18.8	36.8
6-10 Hours (%)	16.6	23.2	20.2	17.6	12.6	17.5	23.5	21.1	31.3	21.1
11-15 Hours (%)	5.3	4.9	10.4	2.9	13.7	10.5	5.9	13.2	12.5	5.3
16 or More Hours (%)	10.1	1.2	7.4	5.9	5.3	7.0	9.8	2.6	6.2	0.0
Strenuous Activities										
0 Hours (%)	80.5	90.2	69.9	72.5	78.9	73.7	74.5	68.4	68.8	73.7
1 Hour (%)	4.7	1.2	13.5	8.7	7.4	10.5	9.8	7.9	18.8	15.8
2-5 Hours (%)	8.9	4.9	8.0	8.7	8.4	10.5	5.9	7.9	9.4	5.3
6-10 Hours (%)	4.1	2.4	4.3	7.2	1.1	3.5	3.9	10.5	0.0	0.0
11-15 Hours (%)	0.6	1.2	1.2	1.4	1.1	0.0	0.0	0.0	0.0	5.3
16 or More Hours (%)	1.2	0.0	3.1	1.4	3.2	1.8	5.9	5.3	3.1	0.0

Table 9-13
Levels of Physical Activity of Participating Transplant Recipients 3, 6, 9, 12 and 15 Months Posttransplant by Primary Renal Diagnosis

	3 Months Posttransplant		6 Months Posttransplant		9 Months Posttransplant		12 Months Posttransplant		15 Months Posttransplant	
	Nondiabetes	Diabetes	Nondiabetes	Diabetes	Nondiabetes	Diabetes	Nondiabetes	Diabetes	Nondiabetes	Diabetes
LIGHT ACTIVITIES										
0 Hours (%)	5.9	13.8	6.2	9.1	7.0	7.9	13.0	5.3	2.8	8.3
1-5 Hours (%)	21.0	18.5	18.9	21.8	17.5	31.8	15.9	31.8	17.9	33.3
6-15 Hours (%)	17.7	40.0	24.3	34.5	25.4	26.3	24.8	21.1	23.1	41.7
16-25 Hours (%)	28.3	18.9	20.3	18.2	28.3	10.5	11.6	28.3	17.9	0.0
26-35 Hours (%)	14.5	4.8	9.0	3.6	10.5	7.9	14.5	5.3	15.4	18.7
36 or More Hours (%)	14.5	8.2	23.2	12.7	13.2	15.8	20.3	10.5	23.1	0.0
Medium Activities										
0 Hours (%)	30.8	47.7	22.7	52.7	29.8	44.7	25.7	31.8	23.1	33.3
1 Hour (%)	11.3	18.9	8.5	5.5	8.8	5.3	7.1	5.3	7.7	8.3
2-5 Hours (%)	22.0	18.5	30.7	18.2	25.4	28.3	27.1	31.8	23.1	33.3
6-10 Hours (%)	21.5	10.8	20.5	18.4	14.0	15.8	25.7	10.5	33.3	8.3
11-15 Hours (%)	6.5	1.5	10.2	1.8	16.7	0.0	7.1	15.8	10.3	8.3
16 or More Hours (%)	8.1	4.6	7.4	5.5	5.3	7.9	7.1	5.3	2.6	8.3
Strenuous Activities										
0 Hours (%)	79.6	95.4	65.0	89.1	74.6	84.2	71.4	73.7	64.1	91.7
1 Hour (%)	4.8	0.0	14.1	5.5	8.8	7.9	10.0	5.3	23.1	0.0
2-5 Hours (%)	9.1	3.1	10.2	1.8	12.3	0.0	5.7	10.5	10.3	0.0
6-10 Hours (%)	4.8	0.0	6.2	1.8	0.9	5.3	5.7	10.5	0.0	0.0
11-15 Hours (%)	1.1	0.0	1.7	0.0	0.9	0.0	0.0	0.0	0.0	8.3
16 or More Hours (%)	0.5	1.5	2.8	1.8	2.6	2.8	7.1	0.0	2.6	0.0

end-stage renal disease (ESRD) patients. In particular, we compare the functional limitations reported by patients in the current study with the functional limitations of patients from the National Kidney Dialysis and Kidney Transplantation Study (NKDKTS) (see Evans et al., 1987). These data were collected from a sample of 859 end-stage renal disease patients associated with 11 dialysis and transplant centers throughout the United States. Of the 859 patients included in the study, 287 were treated with home hemodialysis, 347 were treated with in-center hemodialysis, 81 with continuous peritoneal dialysis (CPD), and 144 with transplantation. Of the 144 transplant patients, 74 had received a transplant from a living related donor, and 70 from a cadaver. It is noteworthy that all kidney transplant recipients in the NKDKTS were on conventional immunosuppressive therapy, consisting of azathioprine (AZA) and prednisone (PRED).

Many of the measures of functional limitations in our current study were also used in the NKDKTS. Not all of the variables examined in this chapter were included in the NKDKTS (for example, NKDKTS patients were not asked questions concerning the amount of time that they spend engaged in light, medium, and strenuous physical activities). However, NKDKTS patients were asked the same series of questions pertaining to their physical limitations at the time the interview was conducted. They were also asked if they were limited in their ability to perform other physical functions such as using their fingers to grasp or handle, using their eyes, and lifting or carrying heavy objects.

Limitations of Daily Activity

Table 9-14 compares the limitations experienced by participating transplant recipients 3 months and 15 months posttransplant with ESRD patients from the National Kidney Dialysis and Kidney Transplantation Study. In addition to presenting the overall percentages of patients reporting various physical limitations, the percentages of patients reporting the various limitations are shown separately by primary renal diagnosis (nondiabetes versus diabetes). The percentages of NKDKTS patients reporting these same limitations are shown overall, as well as by treatment modality.

The results of the National Kidney Dialysis and Kidney Transplantation Study (Evans et al., 1987) concluded that, with the exception of more vision problems among the transplant group (the effect of long-term steroid use), transplant patients with functioning grafts have the lowest levels of functional impairment and in-center hemodialysis and CPD patients have the highest levels of functional impairment. Table 9-14 compares the functional limitations reported by participating transplant recipients 3 and 15 months following transplant surgery with National Kidney Dialysis and Kidney Transplantation Study patients. As can be seen from the table, three months following transplant surgery, transplant patients from the current study report higher levels of functional impairment than NKDKTS transplant patients. By 15 months posttransplant, patients from the current study report levels of disability that are more similar to the levels of impairment reported by transplant patients from the National Kidney Dialysis and Kidney Transplantation Study. For some of the limitations listed in Table 9-14 (e.g., stay in bed most or all of the day because of health, stay indoors most or all of the day because of health), transplant patients in the current study report

Table 9-14
Limitations Experienced by Participating Transplant Recipients 3 Months and 15 Months Posttransplant Compared with National Kidney Dialysis and Kidney Transplantation Study Patients

	Patients 3 Months Posttransplant			Patients 15 Months Posttransplant			National Kidney Dialysis and Kidney Transplantation Study				
BECAUSE OF HEALTH DID PATIENT:	All Patients	Non-Diabetes	Diabetes	All Patients	Non-Diabetes	Diabetes	Home Hemodialysis	In-Center Hemodialysis	Continuous Peritoneal Dialysis	Transplant	All Modalities
Need assistance traveling around community (%)	20.9	10.6	50.8	11.5	2.5	41.7	11.9	25.2	30.9	7.7	18.4
Stay indoors most or all of the day because of health (%)	14.2	12.2	20.0	5.8	5.0	8.3	14.4	19.1	19.8	9.0	15.9
Stay in bed most or all of the day because of health (%)	11.4	9.5	16.9	3.8	5.0	0.0	14.0	19.7	19.8	9.0	16.0
Limited in vigorous activities (%)	74.8	75.1	73.8	80.4	75.0	91.7	88.4	84.7	92.6	66.7	83.6
Trouble walking several blocks or climbing stairs because of health (%)	43.7	39.7	55.4	40.4	37.5	50.0	62.8	70.0	80.2	39.9	63.5
Trouble bending, stooping, or lifting because of health (%)	42.1	39.7	49.2	32.7	32.5	33.3	49.0	57.3	80.2	38.2	53.5
Trouble walking one block or climbing one flight of stairs because of health (%)	27.6	21.7	44.6	19.2	17.5	25.0	31.9	42.6	58.0	17.4	36.2
Help in walking such as another person, cane, crutches, etc. (%)	13.0	6.9	30.8	13.5	5.0	41.7	10.8	21.4	20.0	8.3	15.5
Unable to do certain amounts of work, housework, or schoolwork (%)	48.0	45.0	56.9	48.1	45.0	58.3	65.9	67.7	72.5	38.9	62.7
Unable to work at job or do work around house (%)	43.3	37.0	61.5	40.4	37.5	50.0	50.2	65.7	69.6	29.9	54.8
Need help eating, dressing, bathing, or using toilet (%)	5.1	3.2	10.8	0.0	0.0	0.0	4.2	9.0	14.8	2.1	6.8
Limited in any way from doing anything he wants to (%)	62.2	58.7	72.3	51.9	50.0	58.3	81.9	81.2	85.2	56.9	77.7

lower levels of impairment than NKDKTS transplant patients. With respect to other limitations, such as those requiring help in walking, those unable to work at a job or do work around the house, and those who say they are limited in vigorous activity, transplant patients in the current study report higher levels of disability than NKDKTS transplant patients. It is, however, important to note that compared with NKDKTS dialysis patients, patients from the current study report much lower levels of impairment both 3 and 15 months following transplantation.

A comparison of the limitations experienced by diabetic and nondiabetic patients in the current study with the limitations experienced by patients in the NKDKTS is also presented in Table 9-14. As can be seen in the table, the nondiabetic patients in the current study have lower levels of impairment, similar to the transplant patients in the National Kidney Dialysis and Kidney Transplantation Study. The higher levels of physical impairment reported by the diabetic patients in the current study exceed the levels of impairment of NKDKTS transplant patients. However, the diabetic patients in the current study are less impaired than the NKDKTS dialysis patients.

In comparing the limitations of transplant patients from the current study with transplant patients from the NKDKTS, it is important to consider differences in the characteristics of the patients included in the two studies. Such case-mix differences between the patients in the two studies may explain differences in the limitations reported by patients. One major difference between the transplant patients from the two studies is in the length of time between transplantation and when functional ability was measured. The limitations reported in Table 9-14 are for transplant patients 3 months and 15 months following surgery, whereas the limitations of transplant patients in the NKDKTS were measured an average of 4.28 years following transplantation. Indeed, only 19.4 percent of transplant patients in the NKDKTS sample had received their transplants less than one year prior to data collection. In addition, the average age of the transplant patients in the NKDKTS was 37.2 years compared to 42.2 years for patients in the current study. Finally, 26.5 percent of all patients included in the current study are diabetic patients, compared with only 7.9 percent of transplant patients from the National Kidney Dialysis and Kidney Transplantation Study. Thus, differences in the characteristics of the transplant patients included in the two studies (in particular differences in the length of time since transplantation or in the proportion of diabetic patients) may account for the differences in the reported levels of physical impairment.

Other Physical Limitations

Finally, as discussed earlier, patients in both the current study and the National Kidney Dialysis and Kidney Transplantation Study were asked if they were limited in their ability to perform other physical functions (e.g., using their fingers to grasp or handle, using their eyes for reading or inspection of things, lifting or carrying heavy objects). Table 9-15 compares the limitations reported by transplant recipients from the current study at 3 and 15 months posttransplant with NKDKTS patients. In addition to presenting the overall percentages of patients with various physical limitations, the table also presents the percentages of patients reporting the various limitations separately by primary renal diagnosis (nondiabetes versus diabetes). The percentages of NKDKTS patients reporting these same limitations are shown overall, as well as by treatment modality.

Table 9-15
Percent of Transplant Recipients with Various Functional Limitations 3 Months and 15 Months Posttransplant Compared with National Kidney Dialysis and Kidney Transplantation Study Patients

	Patients 3 Months Posttransplant			Patients 15 Months Posttransplant			National Kidney Dialysis and Kidney Transplantation Study				
	All Patients	Non-Diabetes	Diabetes	All Patients	Non-Diabetes	Diabetes	Home Hemodialysis	In-Center Hemodialysis	Continuous Peritoneal Dialysis	Transplant	All Modalities
Reach (%)	11.8	12.7	9.2	5.8	5.0	8.3	15.4	29.3	24.7	9.0	20.8
Use Fingers to Grasp or Handle (%)	10.2	10.1	10.8	3.8	5.0	0.0	16.1	31.3	19.8	9.0	21.4
Use Eyes For Inspection of Things (%)	25.2	14.3	56.9	42.3	37.5	58.3	18.9	38.0	24.7	31.0	29.2
Use Eyes For Reading (%)	29.1	19.0	58.4	40.4	40.0	41.7	20.0	35.7	28.8	31.3	29.0
Lift or Carry Weights Up to 10 Pounds (%)	22.4	20.6	27.7	11.5	12.5	8.3	28.7	42.0	46.2	14.6	33.3
Lift or Carry Weights Up to 25 Pounds (%)	56.3	55.6	58.5	40.4	45.0	25.0	53.0	62.9	73.7	34.5	57.4
Lift or Carry Weights Up to 50 Pounds (%)	78.7	77.8	81.5	65.4	67.5	58.3	71.3	79.3	91.1	59.6	76.5

With the exception of vision problems, transplant patients in the current study reported a higher level of functional impairment three months following surgery than NKDKTS transplant patients. By 15 months posttransplant, however, transplant patients from the current study reported levels of functional impairment similar to the levels reported by transplant patients from the National Kidney Dialysis and Kidney Transplantation Study. For example, 15 months following transplantation, patients in the current study reported less difficulty reaching, using their fingers to grasp or handle and lifting or carrying weight up to 10 pounds when compared with NKDKTS transplant patients. With respect to using their eyes or lifting or carrying heavier weights, they reported more difficulty than NKDKTS transplant patients. Both 3 and 15 months following their surgery, transplant patients from both studies reported less functional impairment compared with dialysis patients from the National Kidney Dialysis and Kidney Transplantation Study. The only exception is in terms of vision problems which, because of their long-term use of steroids, are higher among transplant patients from both studies. In general, these results are consistent with the findings reported above.

Discussion

In this chapter we examined the rehabilitation of renal transplant recipients following transplant surgery as reflected in their ability to function physically. Patients were asked a series of questions concerning the extent to which they are limited in various physical activities or have specific functional limitations because of their health. Patients were also asked to estimate the amount of time they spend each week engaged in various types of physical activities. Functional impairment was measured at several points in time--at 3-months, 6-months, 9-months, 12-months, and 15-months posttransplant. Information regarding functional impairment one year prior to transplantation was also examined. Differences in functional ability were examined separately for patients in the two initial immunosuppressive protocol groups (AZA + PRED + ALG versus CSA + PRED), and for patients grouped by primary renal diagnosis (diabetes versus nondiabetes).

The results of our analysis show a dramatic improvement in the level of physical functioning of renal transplant patients following transplant surgery when compared with physical functioning one year prior to transplantation. The general functional ability of transplant patients appears to improve gradually during the first 12 months following transplant surgery. The small number of transplant recipients for whom 15-month follow-up data were available limits our ability to determine whether or not the improvements in physical functioning continue beyond 12 months posttransplant.

Following transplantation, diabetic patients are more functionally impaired than nondiabetic patients. However, diabetics also had considerably higher levels of functional impairment prior to transplantation. Interestingly, the data suggest that among nondiabetic patients, much of the improvement in physical functioning occurs in the first three months posttransplant, whereas among diabetic patients the improvement is not apparent until 9-12 months posttransplant. Thus, although nondiabetics report fewer physical limitations following transplant surgery, it is important to emphasize that the level of physical functioning of both groups is greatly improved over their level of functioning one year prior to transplantation.

With respect to initial immunosuppressive protocol, observed differences in functional ability are not great. During each of the follow-up data collection periods the AZA + PRED + ALG patients report slightly higher levels of impairment than CSA + PRED patients. However, we also observed that the AZA + PRED + ALG patients were more limited in their physical functioning than were CSA + PRED patients prior to their transplant surgery.

Following transplant surgery, most transplant recipients engage in light and medium activities, while only a small percentage participate in strenuous physical activity on a regular basis. Clearly, nondiabetic patients are more active physically than nondiabetic patients. However, with the passage of time since their transplant surgery, both diabetics and nondiabetics spend more time engaged in various physical activities.

One obvious exception to the overall improvement in the functional ability of transplant patients following surgery is an increase in vision problems following transplantation. Increased vision problems are, of course, directly related to long-term steroid use among transplant recipients. This is obvious from the increasing frequency with which vision problems are reported over time. Difficulty with their vision is a much more serious problem for diabetic patients. Three months following transplant surgery, diabetic patients reported far more difficulty using their eyes for reading or for inspection of things. Thus, it is likely that many of the vision problems reported by diabetic patients existed prior to transplantation. Interestingly, the vision problems experienced by diabetic patients do not appear to increase with time. Nondiabetic patients, on the other hand, report increased vision problems during their first 15 months posttransplant.

With respect to initial immunosuppressive protocol, both groups report increased problems with their vision, although the problem appears to be greater among AZA + PRED + ALG patients than among CSA + PRED patients. This, however, may reflect the fact that the AZA + PRED + ALG patient group has a higher percentage of diabetic patients than the CSA + PRED patient group.

Finally, when compared with end-stage renal disease patients from the National Kidney Dialysis and Kidney Transplantation Study, transplant patients from the current study reported higher levels of functional impairment three months following transplant surgery. By 15 months posttransplant, patients from the current study had levels of disability similar to the levels of impairment reported by NKDKTS transplant patients. When compared with NKDKTS dialysis patients, however, patients from the current study consistently reported lower levels of functional impairment. In comparing the levels of physical impairment it is important to keep in mind differences in the characteristics of the patients included in the various groups (i.e., case-mix differences), since many of these characteristics could also influence physical functioning. Ideally, in making such comparisons, one should control for differences in factors such as patient age, primary renal diagnosis (i.e., the proportion with diabetes) and, when comparing transplant patients, length of time since transplantation. Given the higher levels of functional impairment that we observed among diabetic patients, it would appear to be particularly important to consider such differences in comparing the levels of physical impairment of transplant patients from various studies.

CHAPTER 10

THE HEALTH STATUS OF KIDNEY TRANSPLANT RECIPIENTS

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CHAPTER 10 THE HEALTH STATUS OF KIDNEY TRANSPLANT RECIPIENTS

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Introduction

The primary goal of all medical treatment is to restore the patient's health. However, in the case of chronic illness such as end-state renal disease (ESRD), this goal is tenuous at best. Although a kidney transplant may represent an immediate improvement in the health status of an ESRD patient, it can not be viewed as a complete "cure." While it is true that the patient no longer requires regular maintenance dialysis, he or she must continue to take immunosuppressive drugs that have a variety of untoward side-effects. These drugs, which are necessary to combat rejection of the transplanted organ, also reduce the body's defenses against other illnesses. Thus, the immunosuppressive therapy associated with the patient's kidney transplant may ultimately threaten the health status of the transplant patient.

In recent years, as pointed out in Chapter 9, the criteria for judging the success of a medical intervention have come to include a number of patient outcomes other than survival. It is quite common to examine factors such as return to work, functional ability, and health status. Clearly, in choosing the best treatment modality for a patient with end-stage renal disease, the goal is either to restore the patient to his or her pretreatment level of health status or to improve the patient's health status to a level that exceeds that at the time treatment was initiated. Since many ESRD patients have other comorbid conditions, such as diabetes, it is particularly important to recognize that return to good health is relative to the patient's condition.

In previous chapters of this report we have examined the employment status (Chapter 8) and the functional ability (Chapter 9) of transplant recipients following transplant surgery. In this chapter we focus our attention on a slightly different, although related, subject--health status. We examine transplant patients' perceived health status, as well as their satisfaction with their health. We also measure health status using two standardized health status measures: the Sickness Impact Profile and the Nottingham Health Profile. These measures reflect physical, as well as psychological, aspects of health status. One particular advantage of the Sickness Impact Profile is that it combines both a physical and psychosocial dimensions into a total health status score.

Variables

To measure perceived health status, patients were asked a series of questions concerning how they rate their health and their level of satisfaction with their health (see Ries, 1983). These include:

- Perceived health status (e.g., excellent, good, fair, poor).
- Health compared with five years ago.
- Health compared with year before transplant.
- Health compared with other people their age.
- Satisfaction with health--on a scale from "1" (completely satisfied) to "7" (completely dissatisfied).

In addition to the measures of perceived health status, two other health status measures were used. These include the Sickness Impact Profile (SIP) and the Nottingham Health Profile (NHP). The Sickness Impact Profile is a standardized questionnaire that measures sickness-related dysfunction. The SIP consists of 136 questions that are grouped into 12 categories, (see Table 10-1) each describing an area of activity in which dysfunctional behavior may occur. Scores are calculated for each of the categories, as well for a psychosocial dimension, a physical dimension, and an overall SIP score. The physical dimension is created by combining the body care and movement,

Table 10-1

Categories and Sample Items From the Sickness Impact Profile

Category	Items Describing Behavior Related to	Selected Items
SR	Sleep and Rest	I sit during much of the day. I sleep or nap during the day.
E	Eating	I am eating no food at all, nutrition is taken through tubes or intravenous fluids. I am eating special or different food.
W	Work	I am not working at all. I often act irritable toward my work associates.
HM	Home Management	I am not doing any of the maintenance or repair work around the house that I usually do. I am not doing heavy work around the house.
RP	Recreation and Pastimes	I am going out for entertainment less. I am not doing any of my usual physical recreation or activities.
A	Ambulation	I walk shorter distances or stop to rest often. I do not walk at all.
M	Mobility	I stay within one room. I stay away from home only for brief periods of time.
BCM	Body Care and Movement	I do not bathe myself at all, but am bathed by someone else. I am very clumsy in body movements.
SI	Social Interaction	I am doing fewer social activities with groups of people. I isolate myself as much as I can from the rest of the family.
AB	Alertness Behavior	I have difficulty reasoning and solving problems, for example, making plans, making decisions, learning new things. I sometimes behave as if I were confused or disoriented in place or time, for example, where I am, who is around, directions, what day it is.
EB	Emotional Behavior	I laugh or cry suddenly. I act irritable and impatient with myself, for example, talk badly about myself, swear at myself, blame myself for things that happen.
C	Communication	I am having trouble writing or typing. I do not speak clearly when I am under stress.

(See Gilson et al., 1979.)

mobility, and ambulation categories. The psychosocial dimension is created by combining the emotional behavior, social interaction, alertness behavior, and communication categories. In principle, total SIP scores range from 0 to 100, with a low score indicating good health status and a high score indicating poor health. As the level of dysfunction experienced by the subject rises, so does the SIP score (Bergner et al., 1981:787; 1984:508; Pollard et al., 1976:146; Bergner et al., 1976:57; 1976:393). In practice, however, the total mean score on the SIP ranges from 2 or 3 for a near typical control sample of the population (Bergner et al., 1981:787) to 35 or 37 for a homebound terminally ill or chronically ill sample (McCusker and Stoddard, 1984:789).

The Nottingham Health Profile is a two-part instrument designed to measure perceived health problems and to assess the extent to which such problems affect the activities of everyday life (Buxton et al., 1985; McDowell and Newell, 1987; McEwen, 1983:75; Hunt and McEwen, 1983:231; Hunt et al., 1980; 1986; O'Brien et al., 1987:137s). Part I consists of 38 statements, to which respondents simply answer "yes" or "no." The items included in Part I relate to six domains of experience: pain, physical mobility, sleep, emotional reactions, energy, and social isolation. A weighted score ranging between 0 and 100 is obtained on each domain: the higher the score, the greater the extent and severity of the problems. Part II explores the effect of the problems on seven areas of daily life: paid employment, jobs around the house, personal relationships, social life, sex life, hobbies, and vacations. Respondents are instructed to indicate whether or not their present state of health is causing problems with the particular activity. Unlike the Sickness

Impact Profile, the Nottingham Health Profile does not result in an overall health status score.

Results

The health status of participating transplant recipients was measured at several points in time--at 3-months, 6-months, 9-months, 12-months, and 15-months posttransplant, although not all health status measures were utilized during each time period. For example, the Sickness Impact Profile was administered at three points in time (3-months, 9-months, and 12-months posttransplant). The Nottingham Health Profile, on the other hand, was administered at 3-months, 6-months, 12-months and 15-months posttransplant. This was done primarily to reduce the burden to respondents, but also to enable us to conduct methodological studies comparing the SIP and the NHP.

In our analysis, we examine differences in the health status measures separately for patients in the two initial immunosuppressive protocol groups (AZA + PRED + ALG versus CSA + PRED), as well as for patients grouped by primary renal diagnosis (diabetes versus nondiabetes). In addition, we examine the extent to which the health status of transplant recipients changes following transplant surgery. Whenever possible we also compare the health status of participating transplant recipients with the health status of other kidney dialysis and kidney transplant patients.

Our discussion of results is divided into three sections. In the first section we examine differences in the health status of patients three months following transplant surgery by initial immunosuppressive protocol, as well as by primary renal diagnosis. In the second section we examine differences in the various health status measures at three-month intervals from 3 to 15 months posttransplant. The final section presents a comparison of the quality of life of participating transplant recipients with patients from the National Kidney Dialysis and Kidney Transplantation Study (see Evans et al., 1987).

Differences by Initial Immunosuppressive Protocol and Primary Renal Diagnosis

In this section we examine several health status measures. These include: (1) perceived health status; (2) health status as measured by the Sickness Impact Profile; and (3) health status as measured by the Nottingham Health Profile. The analysis presented here is descriptive. With the exception of initial immunosuppressive protocol and primary renal diagnosis, no attempt is made to consider other case-mix variables in examining the health status of renal transplant recipients following transplant surgery. .

Perceived Health Status--

Perceived health status is generally regarded as an important aspect of a patient's recovery from a chronic illness such as end-stage renal disease. Table 10-2 summarizes the responses of patients to a series of questions concerning their perceived health status and satisfaction with their health 3 months following transplantation. Responses are shown for all patients. as well as separately by initial immunosuppressive protocol and primary renal diagnosis.

Patients were first asked to rate their health status at various key points in time--three months posttransplant, five years prior, and the year before they had their kidney transplant. When asked how they rated their health three months following surgery, 10.3 percent said their health was

Table 10-2

Perceived Health Status and Satisfaction with Health of Participating Transplant Recipients Three Months Following Transplant Surgery by Initial Immunosuppressive Protocol and Primary Renal Diagnosis

	All Patients	Primary Renal Diagnosis		Initial Immunosuppressive Protocol	
		Nondiabetes	Diabetes	AZA+PRED+ALG	CSA+PRED
Perceived Health					
Excellent	10.3	12.8	3.1	11.8	7.2
Good	46.4	48.1	41.5	45.0	49.4
Fair	36.9	35.8	40.0	36.1	38.6
Poor	6.3	3.2	15.4	7.1	4.8
Health Compared With 5 Years Ago					
Better	38.5	42.8	26.2	38.5	38.6
About the Same	22.6	25.1	15.4	23.1	21.7
Worse	38.9	32.1	58.5	38.5	39.8
Health Compared With Year Before Transplant					
Better	77.0	78.6	72.3	80.5	69.9
About the Same	15.9	16.0	15.4	11.8	24.1
Worse	7.1	5.3	12.3	7.7	6.0
Health Compared With Other People Their Age					
Better	10.0	12.9	1.5	11.2	7.3
About the Same	32.7	38.2	16.9	29.6	39.0
Worse	57.3	48.9	81.5	59.2	53.7
Satisfaction With Health					
Completely Satisfied	11.2	13.4	4.6	13.7	6.0
Very Satisfied	23.5	26.9	13.8	20.8	28.9
Satisfied	37.8	37.6	38.5	35.7	42.2
Neutral	15.9	14.0	21.6	16.7	14.5
Dissatisfied	8.0	5.4	15.4	8.9	6.0
Very Satisfied	1.2	0.0	4.6	0.6	2.4
Completely Dissatisfied	2.4	2.7	1.5	3.6	0.0

"excellent," 46.4 percent said their health was "good," 36.9 percent said their health was "fair," and 6.3 percent said their health was "poor." When asked if their health was better, about the same, or worse three months following transplantation than it was five years ago, 38.5 percent of the patients said "better," 22.6 percent said "about the same," and 38.9 percent said "worse." Finally, patients were asked if their health three months posttransplant was better, about the same, or worse than it was the year before they had their surgery. The vast majority (77.0%) said that their health was better three months posttransplant than it was the year before they had their transplant surgery.

Perhaps not surprisingly, three months following surgery diabetic patients were less likely than nondiabetic patients to say that their health was "excellent" or "good" and more likely to feel that their health was "fair" or "poor." Three months following transplantation the majority of diabetic patients (58.5%) said that their health was worse than five years ago. In contrast, most nondiabetic patients (42.8%) said that their health was better three months posttransplant when compared with five years ago. In comparing their health three months posttransplant with one year prior to transplantation, the vast majority of both diabetic and nondiabetic patients felt that their health three months posttransplant was better; however, diabetic patients were somewhat less likely to say that their health was better and more likely to say that their health was worse than were nondiabetic patients.

With respect to initial immunosuppressive protocol, differences were not as great. As is shown in Table 10-2, patients who initially received AZA + PRED + ALG were more likely than patients who initially received CSA +

PRED to say that their health was "excellent" three months following transplantation. However, the AZA + PRED + ALG patients were also more likely to say that their health was "poor." Similarly, patients who initially received CSA + PRED were less likely than those who initially received AZA + PRED + ALG to say that their health three months posttransplant was better than their health one year prior to transplantation. The patients who initially received CSA + PRED, however, did not feel that their health was worse than one year prior to transplantation. In comparing their health three months posttransplant with five years ago, the responses of the two initial immunosuppressive protocol groups were similar.

Next, patients were asked to compare their health with other people their age. As can be seen in Table 10-2, only 10.0 percent of the patients felt that three months after their transplant surgery their health was better than other people their age, while 32.7 percent felt that it was about the same, and 57.3 percent felt that it was poorer. Again, the vast majority of diabetic patients (81.5%) responded that their health three months following transplantation was worse than other people their age, compared with only 48.9 percent of nondiabetic patients. The responses of the two initial immunosuppressive groups were consistent with their responses to other questions--a lower percentage of the CSA + PRED group reported that their health was better than other people their age and, at the same time, a lower percentage said that their health was worse than other people their age.

Finally, patients were asked how satisfied they were with their health three months after their surgery. The majority of patients indicated some level of positive satisfaction. Their responses were as follows: 11.2 percent said completely satisfied; 23.5 percent said very satisfied; 37.8 percent said satisfied; 15.9 percent said neutral; 8.0 percent said dissatisfied; 1.2 percent said very dissatisfied; and 2.4 percent said completely dissatisfied. Again, diabetic patients expressed a lower level of satisfaction with their health than did nondiabetic patients. Only 4.6 percent of diabetic patients said that they were completely satisfied with their health three months following their surgery, compared with 13.4 percent of nondiabetic patients. With respect to initial immunosuppressive protocol, fewer CSA + PRED patients were complelely satisfied or completely dissatisfied with their health than was the case for the AZA + PRED + ALG patient group.

Sickness Impact Profile--

Table 10-3 presents mean Sickness Impact Profile scores of participating kidney transplant recipients three months following transplant surgery, overall as well as by initial immunosuppressive protocol and primary renal diagnosis. The table presents means scores for each of the 12 SIP categories, as well as a physical dimension score, a psychosocial dimension score, and a total SIP score. Clearly, participating transplant patients reported the highest level of functional impairment (as witnessed by a score of 39.1) in the work category. The next highest scores were reported in the following categories: social interaction (13.9); home management (13.6); recreation and pastimes (13.6); and sleep and rest (11.6). Few limitations, on the other hand, were reported in the eating, body care and movement, and communication categories.

Health status, as measured by the Sickness Impact Profile, did not differ greatly by initial immunosuppressive protocol. In our analysis of functional ability, we observed that patients in the AZA + PRED + ALG group reported slightly higher levels of impairment than CSA + PRED patients,

Table 10-3

Mean Sickness Impact Profile Scores of Participating Transplant Recipients at Three Months Posttransplant by Initial Immunosuppressive Protocol and Primary Renal Diagnosis

	All Patients	Primary Renal Diagnosis		Initial Immunosuppressive Protocol	
		Nondiabetes	Diabetes	AZA+PRED+ALG	CSA+PRED
Sleep and Rest	11.6	10.3	15.3	10.3	14.1
Emotional Behavior	6.1	5.5	7.8	6.2	5.8
Body Care and Movement	3.5	2.1	7.6	3.6	3.4
Home Management	13.6	11.8	19.0	14.0	12.9
Mobility	5.9	4.4	10.1	6.0	5.5
Social Interaction	13.9	12.7	17.3	14.3	12.9
Ambulation	8.1	5.5	15.6	8.6	7.1
Alertness Behavior	8.7	9.2	7.1	8.2	9.7
Communication	3.9	3.5	4.9	4.4	2.9
Work	39.1	36.0	47.9	41.3	34.4
Recreation-Pastimes	13.6	11.8	18.8	14.6	11.6
Eating	2.8	2.5	3.7	2.8	2.9
Physical Dimension[1]	5.1	3.4	10.0	5.3	4.7
Psychosocial Dimension[2]	9.3	8.7	10.8	9.5	8.9
Total SIP	9.3	8.4	13.0	9.8	9.2
Number of Cases	254	189	65	171	83

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[1] Consists of weighted scores from Body Care and Movement, Mobility, and Ambulation categories.

[2] Consists of weighted scores from Emotional Behavior, Social Interaction, Alertness Behavior, and Communication categories.

perhaps because the AZA + PRED + ALG patient group has a higher percentage of diabetic patients than the CSA + PRED group. The slightly higher level of impairment of the AZA + PRED + ALG group is reflected in somewhat higher SIP scores. The total SIP score for patients who initially received AZA + PRED + ALG was 9.8, compared with 9.2 for patients who initially received CSA + PRED. In terms of both the physical and psychological dimensions the scores of the two groups were also similar. With respect to the work category the two initial immunosuppressive protocol groups differed most. As can be seen in Table 10-3, patients who initially received AZA + PRED + ALG had a score of 41.3 in the work category, compared with a score of 34.4 for patients who initially received CSA + PRED. This is consistent with the findings reported in Chapter 8 of this report.

Consistent with the measures of perceived health status reported above, diabetic patients have a lower health status as measured by the Sickness Impact Profile than nondiabetic patients. With the exception of the alertness behavior category, diabetic patients consistently have higher SIP scores, indicating greater functional impairment, than nondiabetic patients. Diabetic patients in the study had a total SIP score of 13.0, compared with a total SIP score of 8.4 for nondiabetic patients. The difference between the two groups is most apparent in the categories that comprise the physical dimension--body care and movement, mobility, and ambulation. The diabetic patients had a mean score of 10.0 on the physical dimension, compared with a mean score of 3.4 for the nondiabetic patients. In the case of the psychosocial dimension--comprised of the emotional behavior, social interaction, alertness behavior, and communication categories--the difference between the two groups was not large. As can be seen in Table 10-3, for the psychosocial dimension the mean scores for the diabetic and nondiabetic patients were 10.8 and 8.7, respectively. Differences between the two groups were also relatively large in the case of the sleep and rest, home management, work, and recreation and pastimes categories. Diabetic patients, for example, had a score of 47.9 for the work category, compared with a score of 36.0 for nondiabetic patients.

Nottingham Health Profile--

Table 10-4 summarizes the Nottingham Health Profile scores of participating transplant recipients three months following transplant surgery, overall and by initial immunosuppressive protocol and primary renal diagnosis. The top of the table provides mean weighted scores along the following dimensions: pain, physical mobility, sleep, emotional reactions, energy, and social isolation. The bottom of the table indicates the percentage of respondents who reported that their state of health caused problems in each of seven major areas. The Nottingham Health Profile does not yield an overall health status score.

Three months following their surgery, the mean weighted scores of participating transplant recipients for the six dimensions listed in the top of Table 10-4 ranged from a high of 20.0 for the energy dimension to a low of 6.7 for the pain dimension. Scores for the emotional reactions, sleep, social interaction, and physical mobility dimensions ranged between 11.1 and 15.7. As shown in the bottom of Table 10-4, 28.9 percent of all transplant patients said that their state of health three months posttransplant caused problems with their work and 29.7 percent said they had problems performing tasks

Table 10-4

Mean Nottingham Health Profile Scores of Participating Transplant Recipients Three Months Following Transplant Surgery by Initial Immunosuppressive Protocol and Primary Renal Diagnosis

	All Patients	Primary Renal Diagnosis		Initial Immunosuppressive Protocol	
		Nondiabetes	Diabetes	AZA+PRED+ALG	CSA+PRED
Section I: Dimension (Mean Weighted Score)					
Energy	20.0	17.7	26.6	19.6	21.0
Pain	6.7	6.6	6.7	7.6	4.7
Emotional Reactions	11.1	11.0	11.5	10.9	11.5
Sleep	15.7	14.2	19.8	14.8	17.6
Social Isolation	13.2	10.1	21.8	13.5	12.5
Physical Mobility	11.3	9.5	16.3	11.7	10.3
Section II: Activities Affected by Health (Percent Responding "Yes")					
Occupation	28.9	23.9	43.1	27.8	31.2
Ability to Perform Tasks Around the Home	29.7	24.5	44.6	27.8	33.7
Personal Relationships	13.3	12.5	15.4	12.4	15.0
Sex Life	40.2	35.7	53.1	40.1	40.5
Social Life	24.9	19.6	40.0	23.7	27.5
Hobbies	31.3	26.6	44.6	32.5	28.7
Vacation	29.3	26.6	36.9	26.6	35.0
Number of Cases	249	184	65	169	80

around the home because of their health. Fewer patients reported that they had problems with personal relationships (13.3%) or with their social life (24.9%). The activity that the greatest number of patients said was affected by their health was their sex life. Over 40 percent of all patients said that their state of health three months posttransplant caused problems with their sex life. A relatively large proportion of patients said that their health affected recreational activities--hobbies (31.3%) and vacation (29.3%).

Initial immunosuppressive protocol makes little difference in the Nottingham Health Profile scores of patients three months following transplantation. However, as expected, differences were observed by primary renal diagnosis. As can be seen in Table 10-4, diabetic and nondiabetic patients did not differ in terms of pain or emotional reactions. But, in terms of energy, social isolation, and physical mobility, diabetic patients had far more problems than nondiabetic patients. Diabetic patients also reported more problems with sleeping than did nondiabetic patients. Moreover, as is shown in Table 10-4, a higher percentage of diabetic patients reported that their state of health caused problems with their work, as well as their ability to perform tasks around the house, than did nondiabetic patients. The percentages of patients who reported that their health affected their sex life, hobbies and vacation were also higher among diabetic patients. In addition, diabetic patients were more likely than nondiabetic patients to report that their health affected their social life. With respect to personal relationships, that is, relationships with people in their own households, the difference between the two groups was small.

Comparing Nottingham Health Profile scores, it is clear that diabetic patients are more limited than nondiabetic patients in performing various physical activites. However, along psychological dimensions (i.e., emotional reactions) and in terms of personal relationships, diabetic patients do not differ from nondiabetic patients. Perhaps because they are more limited in their ability to get out of the house to interact with others, diabetic patients also experience greater social isolation. These results are consistent with our analysis of patient health status as measured by the Sickness Impact Profile.

Changes in Health Status Over Time

In the previous chapter of this report we observed a dramatic improvement in the functional ability of transplant recipients three months following transplant surgery when compared with their functional ability one year prior to transplantation. We also observed that the physical functioning of transplant patients continues to improve during the first 12 months posttransplant. In our analysis of the health status of patients three months following surgery, we found the improvement in physical functioning to be reflected in the perceived health status of transplant patients. Over three-quarters of transplant patients (77.0%) said that their health was better three months posttransplant than it was the year before they had their transplant surgery.

Having examined differences in various measures of health status by initial immunosuppressive protocol and primary renal diagnosis three months following transplant surgery, we now examine whether or not this gradual improvement in the physical functioning of transplant patients is reflected in the various health status measures.

Many of the variables that were used to measure health status at three months following transplantation were also used to measure health status at

6-months, 9-months, 12-months, and 15-months posttransplant. Thus, we are able to determine whether health status, like functional ability, continues to improve in the months following transplantation.

Perceived Health Status--

As we observed in Chapter 9, the functional ability of renal transplant recipients, which improves dramatically in the first three months posttransplant, continues to improve during the period from 3 to 12 months following surgery. Table 10-5 presents the perceived health status of participating transplant recipients at 3, 6, 9, 12, and 15 months posttransplant. In general, the improvements observed in the functional ability of patients following transplantation are reflected in perceived health status of patients. For example, over time there is an increase in the percentage of patients who feel that their health is either excellent or good and a decrease in the percentage who feel that their health is fair or poor. When asked to compare their health three months posttransplant with their health one year prior to their transplant surgery, 77.0 percent of all patients said that their health three months posttransplant was better than one year before transplantation. By 12 months posttransplant, 87.6 percent of all patients said that their health was better than one year before their transplant surgery. Similarly, over time patients were less likely to say that their health was worse than other people their age and more likely to say that their health was about the same or better than other people their age. Also, patients reported being more satisfied with their health with the passage of time (53.9% of patients said that they were completely satisfied or

Table 10-5

Perceived Health Status and Satisfaction with Health of Participating Transplant Recipients at 3, 6, 9, 12, and 15 Months Posttransplant

	3 Months Posttransplant	6 Months Posttransplant	9 Months Posttransplant	12 Months Posttransplant	15 Months Posttransplant
Perceived Health					
Excellent	10.3	13.4	17.8	21.3	13.5
Good	46.4	49.6	46.1	49.4	61.5
Fair	36.9	31.0	30.3	27.0	25.0
Poor	6.3	6.0	5.9	2.2	0.0
Health Compared With Year Before Transplant					
Better	77.0	85.3	81.6	87.6	82.7
About the Same	15.9	9.9	11.8	9.0	11.5
Worse	7.1	4.7	6.6	3.4	5.8
Health Compared With Other People Their Age					
Better	10.0	20.3	9.3	16.9	15.4
About the Same	32.7	63.2	50.3	44.9	50.0
Worse	57.3	16.5	40.4	38.2	34.6
Satisfaction With Health					
Completely Satisfied	11.2	15.5	13.8	21.3	13.5
Very Satisfied	23.5	26.3	30.9	32.6	32.7
Satisfied	37.8	34.9	31.6	20.2	36.5
Neutral	15.9	11.6	14.5	13.5	9.6
Dissatisfied	8.0	9.1	4.6	11.2	3.8
Very Dissatisfied	1.2	2.2	3.9	0.0	3.8
Completely Dissatisfied	2.4	0.4	0.7	1.1	0.0

very satisfied with their health 12 months posttransplant, compared with only 34.7% three months posttransplant).

The perceived health status of participating transplant recipients at 3, 6, 9, 12, and 15 months posttransplant by initial immunosuppressive protocol and primary renal diagnosis are presented in Table 10-6 and Table 10-7, respectively. With respect to initial immunosuppressive protocol, the improvement in the perceived health status of transplant patients is observed for patients who initially received AZA + PRED + ALG, as well as for patients who initially received CSA + PRED. Clearly, the perceived health status of transplant patients reflects the improvement in functional ability of the groups following transplantation.

With respect to primary renal diagnosis, the perceived health status of both diabetic and nondiabetic patients improves in the first 12 months following transplantation. As shown in Table 10-7, patients in both groups are more likely to say that their health is excellent or good, they are more likely to say that their health is better than the year prior to transplantation, and they are less likely to feel that their health is worse than other people their age with the passage of time. Over time, patients in both groups also become more satisfied with their health. As shown in Chapter 9, even after transplantation diabetic patients are more functionally impaired than nondiabetic patients. In this chapter we have seen that, although the perceived health status of diabetic patients improves in the months following transplantation, diabetic patients continue to report a lower perceived health status than nondiabetic patients.

Table 10-6

Perceived Health Status and Satisfaction with Health of Participating Transplant Recipients Following Transplant Surgery by Initial Immunosuppressive Protocol

	3 Months Posttransplant		6 Months Posttransplant		9 Months Posttransplant		12 Months Posttransplant		15 Months Posttransplant	
	AZA+PRED+ALG	CSA+PRED	AZA+PRED+ALG	CSA+PRED	AZA+PRED+ALG	CSA+PRED	AZA+PRED+ALG	CSA+PRED	AZA+PRED+ALG	CSA+PRED
Perceived Health										
Excellent	11.8	7.2	13.5	13.0	21.1	12.3	23.5	18.4	21.2	0.0
Good	45.0	49.4	48.5	52.2	44.2	49.1	43.1	57.9	54.5	73.7
Fair	36.1	38.6	32.5	27.5	29.5	31.6	31.4	21.1	24.2	26.3
Poor	7.1	4.8	5.5	7.2	5.3	7.0	2.0	2.6	0.0	0.0
Health Compared With Year Before Transplant										
Better	80.5	69.9	85.9	84.1	84.2	77.2	84.3	92.1	90.9	68.4
About the Same	11.8	24.1	9.8	10.1	7.4	19.3	9.8	7.9	6.1	21.1
Worse	7.7	6.0	4.3	5.8	8.4	3.5	5.9	0.0	3.0	10.5
Health Compared With Other People Their Age										
Better	11.2	7.3	11.0	16.2	13.7	1.8	19.6	13.2	24.2	0.0
About the Same	29.6	39.0	46.6	32.4	48.4	53.6	45.1	44.7	36.4	73.7
Worse	59.2	53.7	42.3	51.5	37.9	44.6	35.3	42.1	39.4	26.3
Satisfaction With Health										
Completely Satisfied	13.7	6.0	16.0	14.5	13.7	14.0	23.5	18.4	18.2	5.3
Very Satisfied	20.8	28.9	26.4	26.1	33.7	26.3	27.5	39.5	30.3	36.8
Satisfied	35.7	42.2	33.7	37.7	27.4	38.6	23.5	15.8	33.3	42.1
Neutral	16.7	14.5	11.7	11.6	13.7	15.8	13.7	13.2	15.2	0.0
Dissatisfied	8.9	6.0	9.2	8.7	6.3	1.8	9.8	13.2	3.0	5.3
Very Dissatisfied	0.6	2.4	2.5	1.4	5.3	1.8	0.0	0.0	0.0	10.5
Completely Dissatisfied	3.6	0.0	0.6	0.0	0.0	1.8	2.0	0.0	0.0	0.0

Table 10-7

Perceived Health Status and Satisfaction with Health of Participating Transplant Recipients Following Transplant Surgery by Primary Renal Diagnosis

	3 Months Posttransplant		6 Months Posttransplant		9 Months Posttransplant		12 Months Posttransplant		15 Months Posttransplant	
	Nondiabetes	Diabetes	Nondiabetes	Diabetes	Nondiabetes	Diabetes	Nondiabetes	Diabetes	Nondiabetes	Diabetes
Perceived Health										
Excellent	12.8	3.1	17.5	0.0	20.2	10.5	25.7	5.3	17.5	0.0
Good	48.1	41.5	51.4	43.6	47.4	42.1	50.0	47.4	62.5	8.3
Fair	35.8	40.0	27.1	43.6	27.2	39.5	22.9	42.1	20.0	41.7
Poor	3.2	15.4	4.0	12.7	5.3	7.9	1.4	5.3	0.0	0.0
Health Compared With Year Before Transplant										
Better	78.6	72.3	84.2	89.1	83.3	76.3	88.6	84.2	85.0	75.0
About the Same	16.0	15.4	11.9	3.6	8.8	21.1	7.1	15.8	10.0	16.7
Worse	5.3	12.3	4.0	7.3	7.9	2.6	4.3	0.0	5.0	8.3
Health Compared With Other People Their Age										
Better	12.9	1.5	14.8	5.5	8.8	10.5	17.1	15.8	12.5	25.0
About the Same	38.2	16.9	48.3	23.6	58.5	26.3	48.6	31.6	55.0	33.3
Worse	48.9	81.5	36.9	70.9	32.7	63.2	34.3	52.6	32.5	41.7
Satisfaction With Health										
Completely Satisfied	13.4	4.6	18.1	7.3	15.8	7.9	24.3	10.5	15.0	8.3
Very Satisfied	26.9	13.8	28.8	18.2	34.2	21.1	35.7	21.1	35.0	25.0
Satisfied	37.6	38.5	34.5	36.4	30.7	34.2	15.7	36.8	35.0	41.7
Neutral	14.0	21.6	10.2	16.4	11.4	23.7	12.9	15.8	10.0	8.3
Dissatisfied	5.4	15.4	6.8	16.4	3.5	7.9	10.0	15.8	2.5	8.3
Very Dissatisfied	0.0	4.6	1.1	5.5	3.5	5.3	0.0	0.0	2.5	8.3
Completely Dissatisfied	2.7	1.5	0.6	0.0	0.9	0.0	1.4	0.0	0.0	0.0

Sickness Impact Profile--

Table 10-8 presents a comparison of health status, as measured by the Sickness Impact Profile, 3 months, 9 months, and 12 months following transplant surgery. The Sickness Impact Profile was not administered as part of the 6-month and 15-month follow-up surveys. As can be seen from the table, the improvement in physical functioning that we observed during the first year following transplant surgery is, indeed, reflected in the Sickness Impact Profile scores. Three months following transplantation patients had a total SIP score of 9.3. By 9 months posttransplant the total SIP score was 7.5 and by 12 months posttransplant the total SIP score was only 6.7. Both the physical and psychosocical dimension scores improved with the passage of time. Scores for the separate SIP categories also improved with increasing time since transplantation. The score in the work category, which was 39.1 three months posttransplant, was reduced to 28.5 one year following surgery.

Table 10-9 compares mean Sickness Impact Profile scores at 3-months, 9-months, and 12-months posttransplant by initial immunosuppressive protocol. Table 10-10 presents a similar comparison for patients grouped by primary renal diagnosis. The scores of both initial immunosuppressive protocol groups improve over time and there is little difference between the scores of the two groups. Interestingly, the greater work disability of the AZA + PRED + ALG group that was observed three months following surgery is no longer apparent 9-months and 12-months posttransplant.

With respect to primary renal diagnosis, differences in the Sickness Impact Profile scores of the two groups are most dramatic three months following transplant surgery. In the case of nondiabetic patients, SIP scores changed little during the period from 3-12 months posttransplant. Three

Table 10-8

Mean Sickness Impact Profile Scores of Participating Transplant Recipients at 3, 9, and 12 Months Posttransplant

SIP Categories	3 Months Posttransplant	9 Months Posttransplant	12 Months Posttransplant
Sleep and Rest	11.6	5.3	3.6
Emotional Behavior	6.1	5.2	3.9
Body Care and Movement	3.5	3.1	2.9
Home Management	13.6	8.8	9.2
Mobility	5.9	4.5	4.6
Social Interaction	13.9	11.2	11.1
Ambulation	8.1	6.9	6.6
Alertness Behavior	8.7	7.1	6.0
Communication	3.9	3.1	2.0
Work	39.1	34.8	28.5
Recreation-Pastimes	13.6	7.9	7.5
Eating	2.8	2.6	2.5
Physical Dimension[1]	5.1	4.3	4.2
Psychosocial Dimension[2]	9.3	7.6	6.8
Total SIP	9.3	7.5	6.7
Number of Cases	254	152	89

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[1] Consists of weighted scores from Body Care and Movement, Mobility, and Ambulation categories.

[2] Consists of weighted scores from Emotional Behavior, Social Interaction, Alertness Behavior, and Communication categories.

Table 10-9

Mean Sickness Impact Profile Scores of Participating Transplant Recipients at 3, 9, and 12 Months Posttransplant by Initial Immunosuppressive Protocol

SIP Categories	3 Months Posttransplant		9 Months Posttransplant		12 Months Posttransplant	
	AZA+PRED+ALG	CSA+PRED	AZA+PRED+ALG	CSA+PRED	AZA+PRED+ALG	CSA+PRED
Sleep and Rest	10.3	14.1	5.7	4.7	4.2	2.8
Emotional Behavior	6.2	5.8	5.3	5.0	3.9	3.8
Body Care and Movement	3.6	3.4	3.3	2.8	3.2	2.6
Home Management	14.0	12.9	8.8	8.9	8.4	10.2
Mobility	6.0	5.5	4.8	3.9	4.3	5.1
Social Interaction	14.3	12.9	11.6	10.5	11.9	10.0
Ambulation	8.6	7.1	6.9	6.8	7.4	5.5
Alertness Behavior	8.2	9.7	7.6	6.3	6.7	5.1
Communication	4.4	2.9	3.8	2.0	2.2	1.8
Work	41.3	34.4	35.1	34.2	29.8	26.8
Recreation-Pastimes	14.6	11.6	8.9	6.3	7.4	7.6
Eating	2.8	2.9	2.9	2.2	2.2	2.8
Physical Dimension[1]	5.3	4.7	4.5	3.9	4.4	3.8
Psychosocial Dimension[2]	9.5	8.9	8.0	6.8	7.3	6.1
Total SIP	9.8	9.2	7.8	7.0	7.0	6.3
Number of Cases	171	83	95	57	51	38

[1] Consists of weighted scores from Body Care and Movement, Mobility, and Ambulation categories.

[2] Consists of weighted scores from Emotional Behavior, Social Interaction, Alertness Behavior, and Communication categories.

Table 10-10

Mean Sickness Impact Profile Scores of Participating Transplant Recipients at 3, 9, and 12 Months Posttransplant by Primary Renal Diagnosis

SIP Categories	3 Months Posttransplant		9 Months Posttransplant		12 Months Posttransplant	
	Nondiabetes	Diabetes	Nondiabetes	Diabetes	Nondiabetes	Diabetes
Sleep and Rest	10.3	15.3	4.8	6.8	3.4	4.3
Emotional Behavior	5.5	7.8	5.0	5.7	3.9	3.8
Body Care and Movement	2.1	7.6	2.6	4.6	2.6	3.9
Home Management	11.8	19.0	7.9	11.6	8.0	13.1
Mobility	4.4	10.1	3.5	7.1	4.4	5.5
Social Interaction	12.7	17.3	11.4	10.5	11.1	11.0
Ambulation	5.5	15.6	5.0	12.4	5.9	9.1
Alertness Behavior	9.2	7.1	8.3	3.6	7.0	2.3
Communication	3.5	4.9	3.1	3.2	2.3	1.1
Work	36.0	47.9	30.0	48.8	23.2	46.9
Recreation-Pastimes	11.8	18.8	7.0	10.5	7.2	8.5
Eating	2.5	3.7	2.6	2.6	2.5	2.4
Physical Dimension[1]	3.4	10.0	3.3	7.0	3.8	5.5
Psychosocial Dimension[2]	8.7	10.8	7.9	6.7	7.1	5.8
Total SIP	8.4	13.0	6.9	9.3	6.3	8.1
Number of Cases	189	65	113	39	69	20

[1] Consists of weighted scores from Body Care and Movement, Mobility, and Ambulation categories.

[2] Consists of weighted scores from Emotional Behavior, Social Interaction, Alertness Behavior, and Communication categories.

months following transplantation nondiabetic patients had a total SIP score of 8.4. By 12 months posttransplant, the total SIP score of nondiabetic patients was 6.3. Among diabetic patients, however, the improvement was much greater. The total SIP score of diabetic patients in the study, was 8.1 twelve months posttransplant, compared with 13.0 when measured three months after transplant surgery. The physical and psychosocial dimension scores, as well as most of the individual category scores, also show that the differences between diabetic and nondiabetic patients decrease with the passage of time.

The most obvious exception to this general trend is with respect to the work disability category. As can be seen in Table 10-10, the work category score of nondiabetic patients declined from 36.0 at three months posttransplant to 23.2 twelve months following surgery. However, the work category score of diabetic patients changed very little during this same period. These results are consistent with our examination of employment status presented in Chapter 8 of this report.

Thus, with the exception of work disability, the improvement in the health status of diabetic patients during the period from 3-12 months posttransplant was much greater in the case of diabetic patients than it was for nondiabetic patients. This is consistent with our analysis of functional limitations, in which we observed that the improvement in functional ability from 3-12 months posttransplant was most dramatic in the case of the diabetic patient group.

Nottingham Health Profile--

Table 10-11 presents a comparison of health status, as measured by the Nottingham Health Profile, 3 months, 6 months, 12 months and 15 months following transplant surgery. The Nottingham Health Profile was not administered as part of the nine-month follow-up survey. Over time, the mean weighted scores for the six dimensions reported at the top of Table 10-11 show a slight improvement when compared with the scores three months posttransplant. The improvement was most evident with respect to social isolation and sleep. Other dimensions, such as pain, remained essentially unchanged. Similarly, patients reported less difficulty in terms of their job and in performing tasks around the house as time since transplantation increased. Patients also reported an improvement in their sex life and with respect to their social life and recreational activities (e.g., hobbies, vacation). However, there was little change in terms of personal relationships.

Nottingham Health Profile scores of participating transplant recipients at 3, 6, 12, and 15 months posttransplant by initial immunosuppressive protocol and primary renal diagnosis are presented in Table 10-12 and Table 10-13, respectively. In general, when all patients were included in the analysis (Table 10-11), the Nottingham Health Profile showed an improvement in the health status of transplant patients with the passage of time. However, when patients are grouped by initial immunosuppressive protocol or primary renal diagnosis, patterns are difficult to discern. It is most likely that this is a function of the way in which the NHP scores are constructed. The NHP dimensions reported at the top of Tables 10-12 and 10-13 represent the weighted responses to as few as three questions and each of the scores shown at the bottom of the tables represents the patient responses to a single

Table 10-11

Mean Nottingham Health Profile Scores of Participating Transplant Recipients
at 3, 6, 12, and 15 Months Posttransplant

	3 Months Posttransplant	6 Months Posttransplant	12 Months Posttransplant	15 Months Posttransplant
Section I: **Dimension (Mean Weighted Score)**				
Energy	20.0	16.4	19.0	16.8
Pain	6.7	7.7	5.6	8.4
Emotional Reactions	11.1	10.5	8.9	8.8
Sleep	15.7	12.5	9.9	10.0
Social Isolation	13.2	9.0	6.6	6.5
Physical Mobility	11.3	10.7	8.6	9.6
Section II: Activities Affected by Health (Percent Responding "Yes")				
Occupation	28.9	24.8	29.9	19.6
Ability to Perform Tasks Around the Home	29.7	21.6	14.9	27.5
Personal Relationships	13.3	10.8	11.5	13.7
Sex Life	40.2	34.1	39.5	28.0
Social Life	24.9	17.4	14.9	15.7
Hobbies	31.3	22.9	13.8	19.6
Vacation	29.3	18.2	8.0	19.6
Number of Cases	249	232	89	52

Table 10-12

Mean Nottingham Health Profile Scores of Participating Transplant Recipients at 3, 6, 12, and 15 Months Posttransplant by Initial Immunosuppressive Protocol

	3 Months Posttransplant		6 Months Posttransplant		12 Months Posttransplant		15 Months Posttransplant	
	AZA+PRED+ALG	CSA+PRED	AZA+PRED+ALG	CSA+PRED	AZA+PRED+ALG	CSA+PRED	AZA+PRED+ALG	CSA+PRED
Section I: Dimension (Mean Weighted Score)								
Energy	19.6	21.0	16.3	16.6	18.2	20.1	13.9	21.6
Pain	7.6	4.7	7.9	7.1	6.4	4.4	8.6	7.9
Emotional Reactions	10.9	11.5	10.2	11.2	10.0	7.3	8.1	9.9
Sleep	14.8	17.6	12.5	12.6	9.5	10.6	9.2	11.4
Social Isolation	13.5	12.5	8.8	9.7	6.4	7.0	6.4	6.6
Physical Mobility	11.7	10.3	11.2	9.4	9.4	7.6	11.7	5.9
Section II: Activities Affected by Health (Percent Responding "yes")								
Occupation	27.8	31.2	27.2	19.1	35.3	22.2	25.0	10.5
Ability to Perform Tasks Around the Home	27.8	33.7	21.5	22.1	17.6	11.1	25.0	31.6
Personal Relationships	12.4	15.0	9.8	13.2	13.7	8.3	12.5	15.8
Sex Life	40.1	40.5	35.2	31.3	42.0	36.1	21.9	38.9
Social Life	23.7	27.5	18.4	14.9	17.6	11.1	12.5	21.1
Hobbies	32.5	28.7	22.1	25.0	11.8	16.7	18.8	21.1
Vacation	26.6	35.0	17.8	17.7	7.8	8.3	12.5	31.6
Number of Cases	169	80	163	68	51	36	32	19

Table 10-13
Mean Nottingham Health Profile Scores of Participating Transplant Recipients
at 3, 6, 12, and 15 Months Posttransplant by Primary Renal Diagnosis

	3 Months Posttransplant		6 Months Posttransplant		12 Months Posttransplant		15 Months Posttransplant	
	Nondiabetes	Diabetes	Nondiabetes	Diabetes	Nondiabetes	Diabetes	Nondiabetes	Diabetes
Section I: Dimension (**Mean Weighted** Score)								
Energy	17.7	26.6	14.4	23.0	18.1	22.1	16.8	16.7
Pain	6.6	6.7	7.8	7.2	6.6	2.0	8.2	8.8
Emotional Reactions	11.0	11.5	10.5	10.4	10.3	4.3	8.9	8.1
Sleep	14.2	19.8	12.0	14.4	9.9	10.0	10.5	8.6
Social Isolation	10.1	21.8	7.8	12.9	5.1	11.5	5.1	11.0
Physical Mobility	9.5	16.3	9.0	15.9	9.9	4.4	9.6	9.6
Section II: **Activities Affected by Health** (Percent **Responding "Yes"**)								
Occupation	23.9	43.1	22.9	30.9	23.9	50.0	15.4	33.3
Ability to Perform Tasks Around the Home	24.5	44.6	18.2	32.7	13.4	20.0	25.6	33.3
Personal Relationships	12.5	15.4	12.5	5.5	9.0	20.0	10.3	25.0
Sex Life	35.7	53.1	32.2	40.4	39.4	40.0	28.2	27.3
Social Life	19.6	40.0	13.1	30.9	12.0	25.0	10.3	33.3
Hobbies	26.6	44.6	19.3	34.5	12.0	20.0	15.4	33.3
Vacation	26.6	36.9	15.3	25.5	6.0	15.0	12.8	41.7
Number of Cases	184	65	176	55	67	20	39	12

question. In contrast, the number of questions used in computing the 12 SIP categories ranged between 7 and 23, and the total SIP score is based on the responses to 136 questions. Thus, one observes much greater fluctuation in the Nottingham Health Profile scores than in the Sickness Impact Profile scores, especially if the number of patients in a particular patient group (e.g., the number of diabetic patients surveyed 15 months posttransplant) is small. Based on these results, we prefer the SIP as a more sensitive and stable measure of health status.

Comparisons with Other ESRD Patients

In this section we compare the health status of participating renal transplant recipients with data from previous studies of end-stage renal disease (ESRD) patients. In particular, we compare the health status of patients in the current study with the health status of patients from the National Kidney Dialysis and Kidney Transplantation Study (NKDKTS). As described previously, these data were collected from a sample of 859 end-stage renal disease patients associated with 11 dialysis and transplant centers throughout the United States. Of the 859 patients included in the study, 287 were treated with home hemodialysis, 347 with in-center hemodialysis, 81 with continuous peritoneal dialysis (CPD), and 144 with transplantation. Of the 144 transplant patients, 74 had received a transplant from a living related donor, and 70 from a cadaver. All transplant patients were on conventional immunosuppressive therapy.

Many of the health status measures used in our current study were also used in the NKDKTS. Not all of the variables examined in this chapter are available for NKDKTS patients. For example, the Nottingham Health Profile was not used in the National Kidney Dialysis and Kidney Transplantation Study. However, the Sickness Impact Profile was used to measure the health status of NKDKTS patients. The NKDKTS patients were also asked questions regarding their perceived health status at the time the interview was conducted.

Perceived Health Status--

Table 10-14 compares the perceived health status of participating transplant recipients 3 months and 12 months posttransplant with ESRD patients from the National Kidney Dialysis and Kidney Transplantation Study. Rather than presenting the perceived health status of all patients in the current study at 3 and 12 months posttransplant, the responses of patients to the perceived health status questions are shown separately by primary renal diagnosis (nondiabetes versus diabetes). The responses of NKDKTS patients to these same questions are shown overall, as well as by treatment modality.

The results of the National Kidney Dialysis and Kidney Transplantation Study (Evans et al., 1987) concluded that the perceived health status of transplant patients was higher than that of patients on the other treatment modalities. Not surprisingly, transplant patients were also most satisfied with their health. As can be seen in Table 10-14, three months following transplant surgery, transplant patients from the current study perceived their health status to be lower than transplant patients from the National Kidney Dialysis and Kidney Transplantation Study. They also reported being less satisfied with their health than NKDKTS patients. However, by 12 months posttransplant, patients from the current study perceived their health status

Table 10-14
Perceived Health Status and Satisfaction With Health of Participating Transplant Recipients Following Transplant Surgery Compared with National Kidney Dialysis and Kidney Transplantation Study Patients

	3 Months Posttransplant		12 Months Posttransplant		National Kidney Dialysis and Transplantation Study				
	Nondiabetes	Diabetes	Nondiabetes	Diabetes	Home Hemodialysis	In-Center Hemodialysis	Continuous Peritoneal Dialysis	Transplant	All Modalities
Perceived Health									
Excellent	12.8	3.1	25.7	5.3	7.7	9.0	4.9	29.4	11.6
Good .	48.1	41.5	50.0	47.4	46.8	31.9	39.5	43.4	39.5
Fair	35.8	40.0	22.9	42.1	33.8	45.8	35.8	22.4	36.9
Poor	3.2	15.4	1.4	5.3	11.6	13.3	19.8	4.9	12.0
Health Compared With 5 Years Ago									
Better	42.8	26.2	---	---	28.3	22.0	30.9	53.8	30.3
About the Same	25.1	15.4	---	---	24.5	22.5	7.4	28.0	22.7
Worse	32.1	58.5	---	---	47.2	55.5	61.7	18.2	47.1
Health Compared With Other People Their Age									
Better	12.9	1.5	17.1	15.8	8.9	15.3	12.5	11.9	12.3
About the Same	38.2	16.9	48.6	31.6	31.0	35.1	28.2	46.9	34.9
Worse	48.9	81.5	34.3	52.6	60.1	49.5	61.2	41.3	52.8
Satisfaction With Health*									
Completely/Very Satisfied	40.3	18.4	60.0	31.6	16.4	12.5	14.8	36.8	18.1
Satisfied	37.8	38.5	15.7	38.8	40.9	46.7	43.2	45.1	44.2
Neutral	14.0	21.8	12.9	15.8	19.2	15.9	19.8	11.1	16.8
Dissatisfied	5.4	15.4	10.0	15.8	18.5	18.8	14.8	4.2	15.9
Very/Completely Dissatisfied	2.7	6.1	1.4	0.0	4.9	8.1	7.4	2.8	5.3

*To compare with patients from the National Kidney Dialysis and Kidney Transplantation Study the Completely Satisfied and Very Satisfied Categories were combined and the Very Dissatisfied and Completely Dissatisfied categories were combined.

to be much more similar to transplant patients from the National Kidney Dialysis and Kidney Transplantation Study. With respect to their satisfaction with their health, one year following transplant surgery patients in the current study were more satisfied with their health than NKDKTS transplant patients.

A comparison of the perceived health status of diabetic and nondiabetic patients from the current study with the perceived health status of NKDKTS transplant patients is particularly interesting. As can be seen in Table 10-14, the perceived health status of nondiabetic patients in the current study more closely resembles the perceived health status of the transplant patients in the National Kidney Dialysis and Kidney Transplantation Study. The diabetic transplant patients in the current study, on the other hand, more closely resemble the NKDKTS dialysis patients with respect to perceived health status.

In comparing the health status of transplant patients from the current study with transplant patients from the NKDKTS, it is important to consider differences in the characteristics of the patients included in the two studies. Such case-mix differences between the patients in the two studies may explain differences in the health status measures. One major difference between the transplant patients from the two studies is in the length of time between transplantation and when health status was measured. The measures of perceived health status shown in Table 10-14 are for transplant patients 3 months and 12 months following surgery, whereas the perceived health status of transplant patients in the NKDKTS was measured an average of 4.28 years following transplantation. Indeed, only 19.4 percent of transplant patients in the NKDKTS sample had received their transplants less than one year prior to data collection. In addition, the average age of the transplant patients in the NKDKTS was 37.2 years compared to 42.2 years for patients in the current study. Finally, 26.5 percent of all patients included in the current study are diabetic patients, compared with only 7.9 percent of NKDKTS transplant patients. Thus, differences in the characteristics of the transplant patients included in the two studies (in particular differences in the length of time since transplantation or in the proportion of diabetic patients) may account for the differences in the perceived health status.

Sickness Impact Profile--

Table 10-15 compares the Sickness Impact Profile scores of participating transplant recipients at 3 months and 12 months posttransplant with the Sickness Impact Profile scores of end-stage renal disease patients from the National Kidney Dialysis and Kidney Transplantation Study. The National Kidney Dialysis and Kidney Transplantation Study demonstrated that there are large differences in health status as measured by the Sickness Impact Profile between ESRD treatment modality patient groups. The study found that transplant patients had the highest overall health status, followed by home hemodialysis patients, continuous peritoneal dialysis patients, and in-center hemodialysis patients. Three months following transplant surgery, transplant patients in the current study reported higher SIP scores (i.e., lower health status) than NKDKTS transplant patients. One year following their transplant surgery, however, transplant patients in the the current study had SIP scores similar to transplant patients from the National Kidney Dialysis and Kidney Transplantation Study. In general, this was true for both

Table 10.15
Mean Sickness Impact Profile Scores of Participating Transplant Recipients at 3 and 12 Months Posttransplant Compared with National Kidney Dialysis and Kidney Transplantation Study Patients

SIP Categories	3 Months Posttransplant		12 Months Posttransplant		National Kidney Dialysis and Kidney Transplantation Study			
	Nondiabetes	Diabetes	Nondiabetes	Diabetes	Home Hemodialysis	In-Center Hemodialysis	Continuous Peritoneal Dialysis	Transplant
Sleep and Rest	10.3	15.3	3.4	4.3	15.5	21.7	21.6	6.3
Emotional Behavior	5.5	7.8	3.9	3.8	7.9	8.5	10.4	5.0
Body Care and Movement	2.1	7.6	2.6	3.9	4.6	7.7	9.6	2.4
Home Management	11.8	19.0	8.0	13.1	14.7	24.0	23.3	7.5
Mobility	4.4	10.1	4.4	5.5	4.9	10.4	9.0	2.7
Social Interaction	12.7	17.3	11.1	11.0	7.7	11.4	9.4	4.4
Ambulation	5.5	15.6	5.9	9.1	10.8	16.3	17.4	6.2
Alertness Behavior	9.2	7.1	7.0	2.3	6.4	11.2	8.5	5.0
Communication	3.5	4.9	2.3	1.1	2.4	5.7	3.0	1.4
Work	36.0	47.9	23.2	46.9	37.7	45.0	51.0	28.4
Recreation-Pastimes	11.8	18.8	7.2	8.5	18.2	23.7	24.0	9.0
Eating	2.5	3.7	2.5	2.4	8.0	10.2	6.3	3.1
Physical Dimension[1]	3.4	10.0	3.8	5.5	6.1	10.3	11.3	3.3
Psychosocial Dimension[2]	8.7	10.8	7.1	5.8	6.4	9.7	8.2	4.1
Total SIP	8.4	13.0	6.3	8.1	9.5	13.9	13.7	5.5
Number of Cases	189	65	69	20	286	338	81	144

[1] Consists of weighted scores from Body Care and Movement, Mobility, and Ambulation categories.
[2] Consists of weighted scores from Emotional Behavior, Social Interaction, Alertness Behavior, and Communication categories.

diabetic and nondiabetic patients, although in the work category diabetic patients in the current study more closely resembled NKDKTS in-center hemodialysis and continuous peritoneal dialysis patients.

Discussion

Having examined the employment status and functional ability of participating transplant recipients in previous chapters of this report, in this chapter we turned our attention to the health status of patients in the months following their transplant surgery. In addition to using several measures of perceived health status, we also used two standardized measures of health status--the Sickness Impact Profile and the Nottingham Health Profile. Health status was measured at several points in time, from 3 months to 15 months following transplantation. Differences in health status were examined separately for patients in the two initial immunosuppressive protocol groups (AZA + PRED + ALG versus CSA + PRED), and for patients grouped by primary renal diagnosis (diabetes versus nondiabetes).

In general, kidney transplant recipients appear to present a fairly realistic picture of their health status. Three months following surgery, most patients consider their health status to be either good or fair. In addition, patients clearly regard their health status following surgery as improved over the year prior to their transplant. Moreover, although they seem to realize that their health may be poorer than other people their age, overall only 11.6 percent of the patients expressed some level of negative satisfaction with their health.

The results of our previous analyses have shown that with respect to physical functioning (i.e., limitations of daily activity, employment), diabetic patients are more functionally impaired than nondiabetic patients. Therefore, it is not surprising that the perceived health status of diabetic patients is lower than that of nondiabetic patients. Diabetic patients also have lower health status, as measured by the Sickness Impact Profile and the Nottingham Health Profile, than nondiabetic patients. However, the difference between the two groups is most apparent in the dimensions reflecting physical functioning, rather than with respect to psychological dimensions. Diabetic patients also report greater social isolation. Neither perceived health status, nor health status as measured by the standardized health status measures, differed greatly by initial immunosuppressive protocol.

As observed in Chapter 9, the functional ability of renal transplant recipients, improves dramatically in the months following transplantation. In general, the improvements observed in the functional ability of patients following transplantation are reflected in the perceived health status of patients. With respect to primary renal diagnosis, the perceived health status of both diabetic and nondiabetic patients improves over time; however, diabetic patients consistently report lower perceived health status than nondiabetic patients. Similarly, the Sickness Impact Profile scores and the Nottingham Health Profile scores of both diabetic and nondiabetic patients improve over time. However, the improvement in the health status of diabetic patients during the period from 3-12 months posttransplant was much greater in the case of diabetic patients than it was for nondiabetic patients. This is also consistent with our analysis of functional limitations, in which we observed that the improvement in functional ability from 3-12 months posttransplant was most dramatic in the case of the diabetic patient group.

Finally, we compared the health status of transplant patients from the current study with the health status of end-stage renal disease patients from the National Kidney Dialysis and Kidney Transplantation Study. Three months following their surgery, transplant patients from the current study perceived their health status to be lower than NKDKTS transplant patients. However, by 12 months posttransplant, patients from the current study perceived their health status to be much more similar to transplant patients from the National Kidney Dialysis and Kidney Transplantation Study. Also, one year following transplantation, the Sickness Impact Profile scores of the transplant patients from the current study were similar to the scores of NKDKTS transplant patients. With the expection of the work category, this was true for both diabetic and nondiabetic patients. With respect to work disability, diabetic patients in the current study more closely resembled NKDKTS in-center hemodialysis and continuous peritoneal dialysis patients.

CHAPTER 11

THE SUBJECTIVE QUALITY OF LIFE OF KIDNEY TRANSPLANT RECIPIENTS

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Introduction

Recent advances in medical technology have led to a greater interest and concern about the quality of the lives of patients undergoing treatment for chronic illnesses such as end-stage renal disease (Aaronson et al., 1987; Barsky, 1988:414; Coates et al., 1987:1490; Croog et al., 1986:1657; Fowler et al., 1988:3018; Shaw, 1988:10; Tannock. 1987:1534; Wenger et al., 1984; Winslow, 1987:1937; Zweibel, 1988:839; Belzer et al., 1983:99; Evans and Manninen, 1985:1579; Guttmann, 1979:975; Hart and Evans, 1987:117s; Mathew et al., 1983:820; Parfrey et al., 1988:1231; Simmons et al., 1988:481; Wood, 1983). Historically the success of medical interventions has been judged almost solely on the basis of objective indicators such as patient survival, employment status and functional ability (Kraukauer, 1986:245). While objective proxy indicators of life quality, such as disability, employment and rehabilitation, may be an integral part of the patient's quality of life matrix, we find that an assessment of quality of life should also include perceptual or subjective indicators. In measuring the quality of life of renal transplant recipients we feel that it is equally important to measure the patient's subjective experience with their immediate life circumstances (Andrews and Withey, 1974:1; 1976; Campbell et al., 1976; Campbell, 1976:117; Andrews, 1974:279; Rodgers and Converse, 1975:127). In this regard it is appropriate to consider the patient's life satisfaction, general well-being, and happiness as indicators of their quality of life.

In addition to the studies cited above, there have been numerous other attempts to evaluate the quality of life of patients on various forms of treatment for end-stage renal disease (Krakauer, 1986:245; Rosansky, 1983:115; Keown and Stiller, 1988:s145; Kalman et al., 1983:55; Simmons et al., 1984:253;

Evans et al., 1985:553; Evans et al., 1984:1353; Kutner et al., 1986:396; Kjellstrand, 1988:1). Other studies have focused on the rehabilitation of the ESRD patient and methods to enhance patient outcomes (Flores and Callender, 1987:115; Flechner et al., 1983:572; Richardson, 1987:111; Mann, 1985:102; Martino, 1987:107; Carlson et al., 1987:338; Oka et al., 1983:493; Nadel and Clark, 1986:41). Some studies have focused on diabetics and the comparative advantages of various forms of treatment (Larsson, 1985:1; Larsson et al., 1987:109; Khauli et al., 1986:598). Other studies have specifically examined the failed transplant graft experience (Johnson et al, 1982:286; Carosella, 1984:142; Rodin et al., 1985:357; Binik and Devins, 1986:281). Not surprisingly, there has also been criticism of the methods and indicators used to examine quality of life (Churchill et al., 1987:14). Subjective measures continue to be criticized as to both their relevance and their measurability.

Nevertheless, it is becoming increasingly apparent that many of the commonly used objective indicators of quality of life, such as employment status, are more correctly envisioned as determinants of patient life satisfaction, well-being, and happiness (Evans et al., 1985:553; Evans, 1985:61; Evans et al., 1987). While a transplant patient's quality of life, like that of a person in the general population, is at least partially determined by various sociodemographic factors including age, sex, race, and education (Campbell et al., 1976), numerous other factors are likely to have an influence as well. For example, a transplant patient's satisfaction with his/her life circumstances including health status, may in part be determined by his/her level of disability or functional impairment, employment status or work-related disability, and his/her social environment. Thus, these objective indicators of quality of life are perhaps better envisioned as determinants of a renal transplant patient's subjective assessment of his/her life circumstances. While objective life conditions are informative and important, they may in fact bear little or no relationship to subjective life experiences.

Despite the clear value of measuring the subjective aspects of the transplant recipient's quality of life, the activity is controversial. Many clinicians, for example, still feel that the objective measures of quality of life are the only ones with any real significance. It is argued that the subjective indicators are too "soft" and fail to bear any relationship to the real world, that somehow patients simply do not have a good grasp of their subjective life experience. We disagree, as the results of our numerous quality of life studies are consistent with those of other investigators (Johnson et al., 1982:286; Kutner, 1985:1579; Simmons et al., 1988:415; 1984:253; 1985:1577; 1987). In our estimation, as the margin of improvement on objective quality of life narrows, subjective quality of life will take on new meaning for clinicians. The value of the clinical management of patients will very well be gauged by overall improvement in the patients' subjective quality of life.

Previous chapters of this report have focused on several objective measures of the quality of life of renal transplant recipients following transplant surgery. These include employment status (Chapter 8), functional limitations (Chapter 9), and health status (Chapter 10). The measures are considered objective indicators of quality of life because they reflect physical status. In this chapter we examine the quality of life of renal transplant recipients following transplant surgery using several subjective indicators of life quality. These include measures of life satisfaction, patient well-being, and personal adjustment to the transplant. These variables are referred to as subjective indicators of life quality because they reflect emotional rather than physical status.

Variables

To the extent possible, in our analysis we utilize standardized measures of life satisfaction and well-being, such as those developed by Campbell and associates (1976; Campbell and Converse, 1980) at the Institute of Social Research at the University of Michigan. Table 11-1 provides a list of these variables, along with appropriate references to the published literature from which the variables were derived.

Although the interpretation of most of the quality of life variables is straightforward, a few comments are in order concerning their construction. As shown in Table 11-1, the first three subjective indicators of life quality--Index of Psychological Affect, Index of Well-Being, Index of Overall Life Satisfaction--were taken from the Quality of American Life, 1978 survey (Campbell et al., 1976; Campbell and Converse, 1980). The Index of Psychological Affect, based on eight bipolar items, describes how patients feel about their present life, and responses are averaged for a mean score. The Index of Overall Life Satisfaction is also based on bipolar responses. The Index of Well-Being is calculated by combining the Index of Overall Life Satisfaction and the Index of Psychological Affect (giving slightly more weight to the former). Both the Index of Psychological Affect and the Index of Overall Life Satisfaction range from a low of 1.0 (completely dissatisfied) to a high of 7.0 (completely satisfied). The Index of Well-Being ranges between 2.1 and 14.7 where a

Table 11-1
Description of Subjective Quality of Life Indicators

Variable	Range of Values	Reference
Index of Psychological Affect	1.0-7.0	Campbell et al., 1976; 1980
Index of Well-Being	2.1-14.7	Campbell et al., 1976; 1900
Overall Life Satisfaction	1-7	Campbell et al., 1976; 1980
General Well-Being Index	1.0-6.0	Fazio, 1977
Positive Affect Scale	0-5	Bradburn, 1969
Negative Affect Scale	0-5	Bradburn, 1969
Affect Balance Scale	1-9	Bradburn, 1969
General Life Satisfaction	1.0-2.0	Campbell et al., 1976; 1980
Satisfaction With Marriage	1-7	Campbell et al., 1976; 1980
Satisfaction With Family Life	1-7	Campbell et al., 1976; 1980
Satisfaction With Friendships	1-7	Campbell et al., 1976; 1980
Satisfaction With Savings and Investments	1-7	Campbell et al., 1976; 1980
Satisfaction With Standard of Living	1-7	Campbell et al., 1976; 1980
Feeling About Present Life (hard, easy)	1-7	Campbell et al., 1976; 1980
Feeling About Present Life (tied down, free)	1-7	Campbell et al., 1976; 1980

score of 2.1 indicated low well-being and a score of 14.7 indicated high well-being.

Another measure of patient well-being--the General Well-Being Index--was previously used in the Health Interview Survey conducted by the National Center for Health Statistics (Fazio, 1977). This index contains ten questions about various aspects of the patient's life. The responses to the questions are summed and then averaged to obtain a mean index score.

The next three scales--Positive Affect Scale, Negative Affect Scale, and Affect Balance Scale--are based on the work of Bradburn and Caplovitz (1965) who conceptualized psychological well-being as having two dimensions, namely positive and negative affect. To measure affect, respondents were asked to respond to a series of questions concerning different pleasurable and unpleasurable experiences they might have had in the past few weeks (e.g., "During the past few weeks, did you ever feel very lonely or remote from other people?"). The Positive Affect Scale is constructed by summing patient responses to five questions concerning positive feelings or experiences. The Negative Affect Scale, on the other hand, represents the sum of five questions concerning negative feelings or experiences. The Affect Balance Scale, with a few standard adjustments, results from transforming the differences in intensity on the Positive Affect Scale and the Negative Affect Scale.

Positive affect denotes pleasurable experiences or feelings, while negative affect denotes unpleasurable experiences or feelings. Since the two dimensions of affect are independent of one another, knowledge of a person's standing on one dimension does not enable one to predict their position on the other (Bradburn, 1969). Also, since positive and negative affect can be related to other measures of well-being in opposite directions, it is expected that a person high on positive feelings and low on negative feelings would be "very happy," while someone who was low on positive feelings and high on negative feelings would be more likely to be "unhappy." Thus, the Affect Balance Scale is thought to be a good indicator of a person's feelings of well-being.

The remaining subjective quality of life indicators shown in Table 11-1 were also taken from the work of Campbell and colleagues (1976; Campbell and Converse, 1980). With the exception of General Life Satisfaction, which is an average of the individual's responses to three separate questions, the remaining indicators attempt to measure the patient's satisfaction with a specific area of his or her life (e.g. marriage, friendships, standard of living). Satisfaction with marriage, family life, savings and investments, standard of living, and friendships were recorded using a scale ranging between one (completely dissatisfied) and seven (completely satisfied). The two indicators of feelings concerning patient's present life, "hard vs. easy" and "tied down vs. free," are also responses to bipolar items, with values ranging between one and seven.

In addition to these general indicators of life satisfaction and well-being, we also included questions focusing on the transplant recipient's happiness and personal adjustment to the transplant. More specifically, patients were asked questions focusing on their feelings of dependence on others, their level of happiness compared with before transplantation, feelings about their appearance, and the extent to which they felt that the transplant was a mistake.

Results

For the purposes of this analysis, quality of life and personal adjustment were measured at several points in time--at 3-months, 6-months, 9-months, 12-months, and 15-months posttransplant. Differences in the various subjective quality of life indicators are examined separately for patients in the two initial immunosuppressive protocol groups (AZA + PRED + ALG versus CSA + PRED), as well as for patients grouped by primary renal diagnosis (diabetes versus nondiabetes). The longitudinal nature of the study design provides an opportunity to examine the extent to which the quality of life of transplant recipients changes over time. In addition, whenever possible, the quality of life of participating transplant recipients is compared with other kidney dialysis and transplant patients, as well as to the general population of the United States.

The remainder of this section is divided into three sections. In the first section we examine differences in the various quality of life indicators following transplant surgery by initial immunosuppressive protocol, as well as by primary renal diagnosis. In the second section we examine differences in the various quality of life measures at three-month intervals from 3 to 15 months posttransplant. The final section presents a comparison of the quality of life of participating transplant recipients with other kidney dialysis and transplant patients, as well as with the general population.

Differences by Initial Immunosuppressive Protocol and Primary Renal Diagnosis

The concept of quality of life is multidimensional. Thus, no single measure can adequately reflect quality of life. The various quality of life indicators presented in this chapter are intended to measure different aspects of life quality. Several variables--Overall Life Satisfaction, General Well-Being Index, Affect Balance Scale, General Life Satisfaction--are more general measures of life quality. Other variables (e.g., satisfaction with family life, satisfaction with standard of living, feelings of dependence on others, feelings about physical appearance) focus on much more narrowly-defined aspects of one's life experience. To the extent that different variables may reflect the same dimension, the measures, of course, will be correlated.

Our discussion of results is divided into four sections: (1) life satisfaction, happiness, and patient well-being; (2) feelings of dependence on others; (3) feeling about physical appearance; and (4) personal adjustment to the transplant. In assessing these aspects of quality of life, we have greatly benefited from the work of Dr. Roberta Simmons and her colleagues at the University of Minnesota (now at the University of Pittsburgh). The analysis presented here is largely descriptive. With the exception of initial immunosuppressive protocol and primary renal diagnosis, no attempt is made to consider other case-mix differences in examining the quality of life of renal transplant recipients following transplant surgery.

Life Satisfaction, Happiness and Patient Well-Being--

We begin by focusing our attention on life satisfaction, happiness, and general well-being of renal transplant patients following transplant surgery. Using 15 standardized indicators of life quality, described in detail earlier in this chapter, we measured patient well-being and satisfaction with their life in general, as well as with their satisfaction with specific areas of their lives (e.g., satisfaction with friendships, satisfaction with marriage, satisfaction with family life).

Table 11-2 compares several subjective quality of life indicators of the two initial immunosuppressive protocol groups three months following transplant surgery. As the table clearly indicates, no difference exists between the two initial immunosuppressive protocol groups in terms of the 15 various quality of life indicators. However, when the patients are divided based on their primary renal diagnosis, some interesting differences do emerge. Diabetic patients report having a lower quality of life than nondiabetic patients according to each of the quality of life measures shown in Table 11-3. The differences are large enough to be statistically significant in the case of the following eight variables: Index of Psychological Affect, Index of Well-Being, Overall Life Satisfaction, Negative Affect Scale, Affect Balance Scale, General Life Satisfaction, Satisfaction with Family Life, and Feeling About Present Life (tied down, free).

The analysis presented in previous chapters has shown that diabetic patients have a lower quality of life than nondiabetic patients in terms of various objective indicators of life quality. We found that diabetic patients are less likely to be employed, more likely to be functionally impaired, and have lower health status than nondiabetic patients. Perhaps not surprisingly, diabetic patients also report a lower subjective quality of life. In general, they are less satisfied with the quality of their lives and are more likely to feel tied down than are nondiabetic patients.

In addition to the 15 subjective indicators of quality of life examined above, we attempted to measure the overall level of happiness of renal transplant patients, as well as how patients feel their quality of life compares with other people they know. As a general overview of patient quality of life following transplant surgery, patients were asked a very general question

Table 11-2
Subjective Quality of Life Indicators Three Months Following Transplant Surgery by Initial Immunosuppressive Drug Protocol

	AZA + PRED + ALG	CSA + PRED
Index of Psychological Affect	5.33	5.36
Index of Well-Being	10.96	10.94
Overall Life Satisfaction	5.08	5.06
General Well-Being Index	4.75	4.61
Positive Affect Scale	3.55	3.28
Negative Affect Scale	1.77	1.65
Affect Balance Scale	5.83	5.68
General Life Satisfaction	1.71	1.68
Satisfaction With Marriage	5.78	5.63
Satisfaction With Family Life	5.39	5.43
Satisfaction With Friendships	5.37	5.34
Satisfaction With Savings and Investments	4.12	4.10
Satisfaction With Standard of Living	4.96	5.11
Feeling About Present Life (hard, easy)	4.62	4.75
Feeling About Present Life (tied down, free)	4.79	5.00

Table 11-3
Subjective Quality of Life Indicators Three Months Following Transplant Surgery by Primary Renal Diagnosis

	Nondiabetes	Diabetes
Index of Psychological Affect	5.50	4.86
Index of Well-Being	11.23	10.17
Overall Life Satisfaction	5.17	4.82
General Well-Being Index	4.72	4.64
Positive Affect Scale	3.50	3.38
Negative Affect Scale	1.60	2.09
Affect Balance Scale	5.95	5.32
General Life Satisfaction	1.74	1.57
Satisfaction With Marriage	5.77	5.60
Satisfaction With Family Life	5.54	5.03
Satisfaction With Friendships	5.43	5.17
Satisfaction With Savings and Investments	4.17	3.94
Satisfaction With Standard of Living	5.02	4.98
Feeling About Present Life (hard, easy)	4.75	4.39
Feeling About Present Life (tied down, free)	5.07	4.25

about how happy they are these days. As can be seen in Table 11-4, three months posttransplant 25.8 percent of the patients said that they are "very happy," 64.7 percent said they are "pretty happy," and 9.5 percent said they are "not too happy."

Transplant patients were also asked if they feel that, compared to other people they know, they have enjoyed life up to now more than most people, about the same, or less than most people. Three months following transplant surgery, 34.2 percent of the patients said that they have enjoyed life more than most people, 56.5 percent said about the same, and only 9.3 percent said that they have enjoyed life less than most people. In a similar question, patients were asked to compare their quality of life with other people whom they know. As is shown in Table 11-4, 26.6 percent of patients who responded to the question said that their quality of life is better than others they know, 58.7 percent said that they quality of life is about the same, and only 14.7 percent said that their quality of life is lower than others they know.

Again, there is no difference in the level of happiness expressed by patients in the two initial immunosuppressive protocol groups. However, as was true with respect to the subjective indicators of life quality examined previously, diabetic patients are less likely than nondiabetic patients to report being "very happy," and more likely to report being "not too happy." Similarly, diabetic patients are more likely than nondiabetic patients to say that they have enjoyed life less than others they know and to feel that their quality of life was lower than others they know.

Table 11-4
Levels of Happiness Expressed by Participating Transplant Recipients Three Months Following Transplant Surgery by Initial Immunosuppressive Protocol and Primary Renal Diagnosis

	All Patients	Primary Renal Diagnosis		Initial Immunosuppressive Protocol	
		Nondiabetes	Diabetes	AZA + PRED + ALG	CSA + PRED
Level of Happiness					
Very Happy (%)	25.8	28.9	16.9	27.1	23.2
Pretty Happy (%)	64.7	63.6	67.7	63.5	67.1
Not too Happy (%)	9.5	7.5	15.4	9.4	9.8
Enjoyment of Life Compared With Others					
More than Others (%)	34.2	36.5	27.5	36.1	30.2
Amount the Same (%)	56.5	56.5	56.5	55.2	59.3
Less than Others (%)	9.3	7.0	15.9	8.7	10.5
Quality of Life Compared With Others (%)					
Better (%)	26.6	27.3	24.6	26.5	26.8
About the Same (%)	58.7	61.0	52.3	59.4	57.3
Lower (%)	14.7	11.8	23.1	14.1	15.9

Feelings of Dependence on Others--

Dependence on others can be a serious problem among patients with chronic medical conditions. Transplant recipients were asked a series of questions concerning their dependence on others because of their health (Table 11-5). These questions were borrowed from the work of Simmons and her co-workers (1987). When asked how independent they feel they are in terms of managing their lives, three months posttransplant the vast majority of transplant patients said that they are either very independent (40.3%) or pretty independent (48.2%). Overall, 7.9 percent indicated that they are not very independent and only 3.6 percent said they are not at all independent. However, as is shown in Table 11-5, diabetic patients regard themselves as considerably less independent than nondiabetic patients in managing their lives. While 45.7 percent of nondiabetic patients indicated that they are very independent, only 24.6 percent of diabetic patients reported that they are very independent. Similarly, 3.4 percent of nondiabetic patients, compared with 21.5 percent of diabetic patients, responded that they are not very independent in managing their lives. There is little difference in the level of independence reported by the two initial immunosuppressive protocol groups.

Patients were also asked the extent to which they need extra help getting things done because of their health. As shown in Table 11-5, three months following their surgery, only 5.5 percent of the patients feel that they need a lot of extra help to get things done because of their health, 22.2 percent feel that they need some extra help to get things done, 31.2 percent feel that they need a little extra help, and 41.1 percent feel that they need no more help than any healthy person. Again, diabetic patients were much

Table 11-5
Problems of Dependence on Others of Participating Transplant Recipients Three Months Following Transplant Surgery by Initial Immunosuppressive Protocol and Primary Renal Diagnosis

	All Patients	Primary Renal Diagnosis		Initial Immunosuppressive Protocol	
		Nondiabetes	Diabetes	AZA + PRED + ALG	CSA + PRED
Degree of Independence					
Very indedependent (%)	40.3	45.7	24.6	38.6	43.9
Pretty independent (%)	48.2	47.3	50.8	49.7	45.1
Not very independent (%)	7.9	3.4	21.5	8.2	7.3
Not at all independent (%)	3.6	3.7	3.1	3.5	3.7
Feelings About Dependence					
Are more dependent than would like to be (%)	36.9	29.9	56.9	34.1	42.7
Would like to have someone to depend on more (%)	6.7	6.4	7.7	4.7	11.0
Neither (%)	56.3	63.6	35.4	61.2	46.3
Extra Help Needed Because of Health					
A lot of extra help (%)	5.5	3.7	10.8	5.8	4.9
Some extra help (%)	22.2	18.1	33.8	18.7	29.3
A little extra help (%)	31.2	31.4	30.8	33.3	26.8
No more help than a healthy person (%)	41.1	46.8	24.6	42.1	39.0

more likely to report that they need a lot of extra help or a little more extra help than were nondiabetic patients. Initial immunosuppressive protocol, on the other hand, does not influence patient responses.

Finally, when asked about their dependence on others, over one-third (36.9%) said that they are more dependent on others for help than they would like to be, while 6.7 percent said that they would like to have someone they could depend on more. The majority of patients (56.3%) held neither of these opinions, suggesting that dependence on others is not viewed as a major problem among most renal transplant recipients. However, dependence upon others does appear to be a problem among one subgroup of transplant patients--diabetic patients. Consistent with responses to other questions, over one-half of diabetic transplant recipients (56.9%) say that they are more dependent on others for help than they would like to be, compared with only 29.9 percent of nondiabetic patients. The effect of initial immunosuppressive protocol is less clear. As shown in Table 11-5, a higher percentage of CSA + PRED patients than AZA + PRED + ALG patients reported that they are more dependent on others than they would like to be; however, a higher percentage also say that they would like to have someone to depend upon more.

Feelings About Physical Appearance--

One of the negative side effects of the immunosuppressive therapy following transplantation is a change in the patient's physical appearance. Simmons et al. (1987) have reported extensively on this aspect of the quality of life of transplant recipients. Responses to a series of questions concerning patients' feelings about their physical appearance three months following transplant surgery are summarized in Table 11-6. When patients were asked if they feel that the transplant affects the way they look, 65.0 percent of the patients responded "yes" and 35.0 percent responded "no." Responses to this question did not differ by primary renal diagnosis or by initial immunosuppressive protocol. Diabetic patients, however, were less likely to feel that they were too fat (36.9%) than were nondiabetic patients (50.8%).

As can be seen in Table 11-6, when asked how they feel about the way they look, most patients said that they are either "very happy" (21.3%) or "pretty happy" (55.7%). Only 15.8 percent of patients said that they are "not very happy" and 6.7 percent of patients said that they are "not at all happy" with their physical appearance. Thus, with respect to changes in their physical appearance as a result of their transplant experience, most patients appear to have adjusted well.

Personal Adjustment to the Transplant--

Three months following transplant surgery, the overwhelming majority of participating kidney transplant recipients perceive themselves as having adjusted well to their transplant (Table 11-7). When asked a very general question about how well they think they have adjusted, 71.1 percent of the patients said "very well" and 28.1 percent said "fairly well." Only two patients (0.8%) said "not too well." No patient said that he or she has adjusted either "fairly poorly" or "very poorly."

Patients were then asked to indicate whether the time since they received their transplant has been about what they expected, worse than they expected, or better than they expected. Most patients responded that the time has been either better than they expected (43.5%) or about what they

Table 11-6
Feelings About Appearance of Participating Transplant Recipients Three Months Following Transplant Surgery by Initial Immunosuppressive Protocol and Primary Renal Diagnosis

	All Patients	Primary Renal Diagnosis		Initial Immunosuppressive Protocol	
		Nondiabetes	Diabetes	AZA + PRED + ALG	CSA + PRED
Does Transplant Affect Appearance					
Yes (%)	65.0	64.0	67.7	66.7	61.4
No (%)	35.0	36.0	32.3	33.3	38.6
Do You Think You Are:					
Too fat (%)	47.2	50.8	36.9	49.7	42.2
Just right (%)	42.9	40.2	50.8	43.3	42.2
Too thin (%)	9.8	9.0	12.3	7.0	15.7
Feelings About Appearance					
Very happy (%)	21.3	22.3	18.5	19.4	25.6
Pretty happy (%)	55.7	55.3	56.9	57.1	53.7
Not very happy (%)	15.8	17.0	12.3	16.5	14.6
Not at all happy (%)	6.7	5.3	10.8	7.1	6.1

Table 11-7
Personal Adjustment of Participating Transplant Recipients Three Months Following Transplant Surgery by Initial Immunosuppressive Protocol and Primary Renal Diagnosis

	All Patients	Primary Renal Diagnosis		Initial Immunosuppressive Protocol	
		Nondiabetes	Diabetes	AZA + PRED + ALG	CSA + PRED
Now Well Adjusted To Transplant					
Very well	71.1	70.7	72.3	70.6	72.3
Fairly well	28.1	28.2	27.7	28.8	26.5
Not too well	0.8	1.1	0.0	0.6	1.2
Fairly poorly	0.0	0.0	0.0	0.0	0.0
Very poorly	0.0	0.0	0.0	0.0	0.0
Time Since Transplant Has Been					
About what expected	42.7	45.2	35.4	44.7	38.6
Worse than expected	13.8	13.3	15.4	11.2	19.3
Better than expected	43.5	41.5	49.2	44.1	42.2
How Often Felt Transplant A Mistake					
Never	77.1	75.0	83.1	78.8	73.5
Almost never	11.9	13.3	7.7	11.8	12.0
Sometimes	8.7	8.5	9.2	6.5	13.3
Very often	1.6	2.1	0.0	1.8	1.2
Always	0.8	1.1	0.0	1.2	0.0
Happiness Compared With Before Transplant					
Happier than before transplant	75.6	76.2	73.8	80.1	66.3
Less happy than before transplant	2.8	2.6	3.1	2.9	2.4
About as happy as before	20.1	19.0	23.1	15.8	28.9
Can't remember	1.6	2.1	0.0	1.2	2.4

expected (42.7%). Only 13.8 percent of participating transplant recipients said that the time has been worse that they expected. As shown in Table 11-7, when patients were asked to compare themselves three months following transplant surgery with before they had their transplant, 75.6 percent said that they are generally happier than they were before they had their transplant, 20.1 percent said that they are about as happy as they were before, and only 2.8 percent said that they are less happy. Four patients (1.6%) could not remember how they felt before their surgery.

Finally, all patients were asked to think back over the time since they received their transplant and to indicate how often they have felt that it was a mistake to have a transplant. Over three-quarters (77.1%) responded "never," and 11.9 percent responded "almost never." Three months posttransplant, 8.7 percent of the patients reported that they "sometimes" felt that the transplant was a mistake, four patients (1.6%) felt that their transplant was a mistake "very often," and two patients (0.8%) said that they "always" have felt that it was a mistake to have a transplant.

Clearly, three months following transplant surgery, patients consistently report that they are happy with their kidney transplants. Unlike many of the subjective indicators of life quality examined earlier, patient responses do not vary by primary renal diagnosis. Although diabetic patients report having a lower quality of life than nondiabetic patients according to several of the subjective quality of life measures examined earlier, diabetic patients are somewhat more likely than nondiabetic patients to indicate that the time since their transplant has been better than they expected. Diabetic patients are also more likely than nondiabetic patients to say that they have never felt that their transplant was a mistake. It is, however, important to note that the differences between the two groups are not large. As was true with respect to the various other subjective quality of life measures, initial immunosuppressive protocol has no effect on the personal adjustment variables included in our analysis.

Changes in Quality of Life Over Time

Having examined differences in a variety of subjective quality of life variables by initial immunosuppressive protocol and primary renal diagnosis three months following transplant surgery, we now turn our attention to the question of whether or not the various subjective quality of life indicators change in the months following transplantation. As described in detail in Chapter 3, in addition to the Baseline Patient Questionnaire, which was administered three months posttransplant, Follow-up Patient Questionnaires were administered at 6, 9, 12, and 15 months posttransplant. Since many of the same quality of life variables were measured at 3-months, 6-months, 9-months, 12-months, and 15-months posttransplant, we are able to examine the extent to which the quality of life of transplant recipients changes over time.

Life Satisfaction. Happiness and Patient Well-Being--

In previous chapters of this report we observed changes in various objective indicators of life quality (e.g. employment status. functional impairment. health status) of renal transplant recipients in the months following transplant surgery. In this section we examine life satisfaction. happiness and general well-being of transplant recipients to determine if changes in the objective measures of quality of life are reflected in these more subjective indicators of life quality. First, we examine transplant patients' quality of life following transplant surgery as measured by 10 of the 15 subjective indicators reported in Tables 11-2 and 11-3. The five additional subjective quality of life indicators shown in Tables 11-2 and 11-3 were not included on the Follow-up Patient Questionnaires and, as such, changes in these variables could not be examined over time.

Tables 11-8 and 11-9 present information concerning transplant patients' quality of life at 3, 6, 9, 12, and 15 months posttransplant by initial immunosuppressive protocol and by primary renal diagnosis, respectively. Although patient quality of life appears to improve following transplant surgery when measured by various objective indicators, there is surprisingly little variation in the subjective quality of life measures over time. In general the measures shown in Tables 11-8 and 11-9 are quite stable, showing either little change or a very slight improvement in subjective quality of life in the first nine months following transplant surgery. The quality of life indicators measured at 12 and 15 months posttransplant indicate less stability; however, this may simply be a reflection of the smaller number of respondents for whom data were collected (84 in the case of the 12-month follow-up and 51 in the case of the 15-month follow-up).

Next, we examine the overall level of happiness reported by renal transplant patients at three-month intervals following surgery, as well as how patients feel their quality of life compares with other people they know. Tables 11-10 and 11-11 show the levels of happiness as expressed by participating transplant recipients at 3, 6, 9, 12, and 15 months posttransplant by initial immunosuppressive protocol and by primary renal diagnosis. Clearly, with increasing time since their transplant surgery, patients are much more likely to report that they are "very happy" and less likely to report that they

Table 11-8
Subjective Quality of Life Indicators 3, 6, 9, 12, and 15 Months Posttransplant by Initial Immunosuppressive Protocol

	Months Posttransplant				
	3 Months	6 Months	9 Months	12 Months	15 Months
Overall Life Satisfaction					
AZA+PRED+ALG	5.08	5.21	5.40	5.61	5.30
CSA+PRED	5.06	5.37	5.00	5.50	5.42
General Well-Being Index					
AZA+PRED+ALG	4.75	4.79	4.82	4.92	4.74
CSA+PRED	4.61	4.94	4.80	5.06	4.83
Positive Affect Scale					
AZA+PRED+ALG	3.55	3.19	3.38	4.06	3.55
CSA+PRED	3.28	3.22	3.07	3.86	3.22
Negative Affect Scale					
AZA+PRED+ALG	1.77	1.39	1.33	1.29	1.85
CSA+PRED	1.65	1.15	1.24	0.86	1.28
Affect Balance Scale					
AZA+PRED+ALG	5.83	5.91	6.13	6.83	5.79
CSA+PRED	5.68	6.12	5.95	7.00	6.00
Satisfaction With Marriage					
AZA+PRED+ALG	5.78	5.60	5.59	5.86	5.27
CSA+PRED	5.63	5.79	5.48	5.79	5.76
Satisfaction With Family Life					
AZA+PRED+ALG	5.39	5.31	5.43	5.66	5.36
CSA+PRED	5.43	5.59	5.02	5.55	5.47
Satisfaction With Friendships					
AZA+PRED+ALG	5.37	5.34	5.48	5.55	5.45
CSA+PRED	5.34	5.50	5.04	5.26	5.37
Satisfaction With Savings and Investments					
AZA+PRED+ALG	4.12	4.11	4.22	4.45	4.22
CSA+PRED	4.10	4.29	4.18	4.53	4.26
Satisfaction With Standard of Living					
AZA+PRED+ALG	4.96	4.96	5.14	5.29	5.39
CSA+PRED	5.11	4.96	4.86	5.18	5.05

Table 11-9
Subjective Quality of Life Indicators 3, 6, 9, 12, and 15 Months Posttransplant by Primary Renal Diagnosis

	Months Posttransplant				
	3 Months	6 Months	9 Months	12 Months	15 Months
Overall Life Satisfaction					
Nondiabetes	5.17	5.33	5.24	5.71	5.45
Diabetes	4.82	5.02	5.29	5.00	5.00
General Well-Being Index					
Nondiabetes	4.72	4.83	4.81	4.92	4.77
Diabetes	4.64	4.86	4.83	5.19	4.79
Positive Affect Scale					
Nondiabetes	3.50	3.22	3.26	3.97	3.49
Diabetes	3.38	3.13	3.25	4.00	3.25
Negative Affect Scale					
Nondiabetes	1.60	1.28	1.20	1.18	1.79
Diabetes	2.09	1.43	1.58	0.84	1.17
Affect Balance Scale					
Nondiabetes	5.95	6.02	6.17	6.82	5.77
Diabetes	5.32	5.81	5.72	7.21	6.17
Satisfaction With Marriage					
Nondiabetes	5.77	5.73	5.59	5.94	5.61
Diabetes	5.60	5.41	5.38	5.39	5.00
Satisfaction With Family Life					
Nondiabetes	5.54	5.44	5.29	5.72	5.53
Diabetes	5.03	5.24	5.24	5.21	5.00
Satisfaction With Friendships					
Nondiabetes	5.43	5.38	5.37	5.53	5.55
Diabetes	5.17	5.43	5.16	5.05	5.00
Satisfaction With Savings and Investments					
Nondiabetes	4.17	4.18	4.14	4.47	4.33
Diabetes	3.94	4.11	4.40	4.53	3.91
Satisfaction With Standard of Living					
Nondiabetes	5.02	4.93	5.04	5.34	5.35
Diabetes	4.98	5.06	5.00	4.90	5.00

Table 11-10
Levels of Happiness Expressed by Participating Transplant Recipients 3, 6, 9, 12, and 15 Months Following Transplant Surgery by Initial Immunosuppressive Protocol

	3 Months Posttransplant		6 Months Posttransplant		9 Months Posttransplant		12 Months Posttransplant		15 Months Posttransplant	
	AZA+PRED+ALG	CSA+PRED	AZA+PRED+ALG	CSA+PRED	AZA+PRED+ALG	CSA+PRED	AZA+PRED+ALG	CSA+PRED	AZA+PRED+ALG	CSA+PRED
Level of Happiness										
Very Happy (%)	27.1	23.2	36.2	41.2	34.7	28.1	49.0	36.8	42.4	31.6
Pretty Happy (%)	63.5	67.1	54.0	51.5	57.9	61.4	45.1	60.5	48.5	57.9
Not too Happy (%)	9.4	9.8	9.8	7.4	7.4	10.5	5.9	2.6	9.1	10.5
Quality of Life Compared With Others										
Better (%)	26.5	26.8	20.9	19.1	18.9	25.5	29.4	26.3	34.4	5.3
About the Same (%)	59.4	57.3	62.6	64.7	63.2	60.0	54.9	63.2	43.8	84.2
Lower (%)	14.1	15.9	16.6	16.2	17.9	14.5	15.7	10.5	21.9	10.5

Table 11-11
Level of Happiness Expressed by Participating Transplant Recipients 3, 6, 9, 12, and 15 Months Following Transplant Surgery by Primary Renal Diagnosis

	3 Months Posttransplant		6 Months Posttransplant		9 Months Posttransplant		12 Months Posttransplant		15 Months Posttransplant	
	Nondiabetes	Diabetes	Nondiabetes	Diabetes	Nondiabetes	Diabetes	Nondiabetes	Diabetes	Nondiabetes	Diabetes
Level of Happiness										
Very Happy (%)	28.9	16.9	38.6	34.5	33.3	28.9	44.3	42.1	42.5	25.0
Pretty Happy (%)	63.6	67.7	55.1	47.3	58.8	60.5	51.4	52.6	50.0	58.3
Not too Happy (%)	7.5	15.4	6.3	18.2	7.9	10.5	4.3	5.3	7.5	16.7
Quality of Life Compared With Others										
Better (%)	27.3	24.6	21.0	18.2	18.6	29.7	24.3	42.1	23.1	25.0
About the Same (%)	61.0	52.3	65.9	54.5	64.6	54.1	61.4	47.4	56.4	66.7
Lower (%)	11.8	23.1	13.1	27.3	16.8	16.2	14.3	10.5	20.5	8.3

are "pretty happy." However, the percentage reporting that they are "not too happy" does not vary much with the passage of time. This holds true for both diabetics and nondiabetics, as well for patients regardless of their initial immunosuppressive protocol.

With the exception of the 12-month and 15-month follow-up surveys (in which the variation in responses most likely reflects a smaller sample size), there is little change in terms of how transplant recipients feel their quality of life compares with other people they know. One possible exception is that with the passage of time since their transplant surgery, diabetic patients appear somewhat less likely to feel that the quality of their life is lower, and more likely to feel that the quality of their life is about the same as other people they know (Table 11-11).

Our previous analyses have shown that in terms of employment status, functional impairment, and health status, the quality of life of renal transplant patients improves over time in the months following transplant surgery. However, the improvement in these outcome variables is not reflected in reported levels of life satisfaction, happiness, and general well-being. Indeed, we observed very little change in patients' subjective quality of life following transplantation. In general this was true for all patients, regardless of initial immunosuppressive protocol or primary renal diagnosis. These results are consistent with previous research suggesting that, although they are positively correlated, the level of correlation between various objective and subjective indicators of life quality is not high (Evans et al., 1985; Evans, 1985:61).

Feelings of Dependence on Others--

As discussed earlier, three months following transplant surgery most patients feel that they are either very independent or pretty independent in managing their lives, and most patients do not feel that dependence on others is a serious problem. And, as is shown in Tables 11-12 and 11-13, dependence on others is viewed by patients as even less of a problem over time. In general, as time since transplantation increases, patients are somewhat more likely to say that they are very independent and less likely to say that they are not at all independent in managing their own lives. Similarly, as the time since transplantation increases, patients are less likely to say that they are more dependent on others than they would like, and also less likely to say that they would like to have someone to depend on more. However, perhaps the best reflection of decreased feelings of dependence among transplant recipients can be seen in responses to the question regarding the amount of help patients feel they need because of their health. As time since transplantation increases, patients are far more likely to say that they need no more help than a healthy person. Transplant patient's feelings of dependence on others appear to decline over time, regardless of initial immunosuppressive protocol (Tables 11-12) or primary renal diagnosis (Table 11-13). It is important to recognize, however, that diabetic patients continue to feel much more dependent on others than nondiabetic patients during the entire follow-up period.

Feelings About Physical Appearance--

In general, we concluded that three months following transplant surgery, most patients appear to have adjusted well to changes in their physical

Table 11-12
Problems of Dependence on Others of Participating Transplant Recipients 3, 6, 9, 12, and 15 Months Following Transplant Surgery by Initial Immunosuppressive Protocol

	3 Months Posttransplant		6 Months Posttransplant		9 Months Posttransplant		12 Months Posttransplant		15 Months Posttransplant	
	AZA+PRED+ALG	CSA+PRED	AZA+PRED+ALG	CSA+PRED	AZA+PRED+ALG	CSA+PRED	AZA+PRED+ALG	CSA+PRED	AZA+PRED+ALG	CSA+PRED
Degree of Independence										
Very independent (%)	38.6	43.9	40.5	47.8	33.7	33.9	51.0	55.3	43.8	42.1
Pretty independent (%)	49.7	45.1	49.1	42.0	55.8	53.6	41.2	42.1	50.0	42.1
Not very independent (%)	8.2	7.3	6.7	8.7	7.4	10.7	3.9	2.6	6.3	15.8
Not at all independent (%)	3.5	3.7	3.7	1.4	3.2	1.8	3.9	0.0	0.0	0.0
Feelings About Dependence										
Are more dependent than would like to be (%)	34.1	42.7	28.8	29.0	28.4	33.9	29.4	23.7	31.3	31.6
Would like to have someone to depend on more (%)	4.7	11.0	4.9	5.8	4.2	5.4	3.9	5.3	3.1	5.3
Neither (%)	61.2	46.3	66.3	65.2	67.4	60.7	66.7	71.1	65.6	63.2
Extra Help Needed Because of Health										
A lot of extra help (%)	5.8	4.9	6.1	7.2	3.2	3.5	2.0	2.6	6.3	0.0
Some extra help (%)	18.7	29.3	17.2	14.5	15.8	22.8	17.6	23.7	21.9	31.6
A little extra help (%)	33.3	26.8	22.1	26.1	28.4	26.3	19.6	10.5	9.4	21.1
No more help than a healthy person (%)	42.1	39.0	54.6	52.2	52.6	47.4	60.8	63.2	62.5	47.4

Table 11-13

Problems of Dependence on Others of Participating Transplant Recipients 3, 6, 9, 12, and 15 Months Following Transplant Surgery by Primary Renal Diagnosis

	3 Months Posttransplant		6 Months Posttransplant		9 Months Posttransplant		12 Months Posttransplant		15 Months Posttransplant	
	Nondiabetes	Diabetes	Nondiabetes	Diabetes	Nondiabetes	Diabetes	Nondiabetes	Diabetes	Nondiabetes	DIABETES
Degree of Independence										
Very independent (%)	45.7	24.6	48.0	25.5	38.1	21.1	58.6	31.6	48.7	25.0
Pretty independent (%)	47.3	50.8	44.6	54.5	52.2	63.2	35.7	63.2	46.2	50.0
Not very independent (%)	3.4	21.5	5.1	14.5	7.1	13.2	2.9	5.3	5.1	25.0
Not at all independent (%)	3.7	3.1	2.3	5.5	2.7	2.6	2.9	0.0	0.0	0.0
Feelings About Dependence										
Are more dependent than would like to be (%)	29.9	56.9	23.7	45.5	23.9	50.0	21.4	47.4	23.1	58.3
Would like to have someone to depend on more (%)	6.4	7.7	4.0	9.1	3.5	7.9	4.3	5.3	5.1	0.0
Neither (%)	63.6	35.4	72.3	45.5	72.6	42.1	74.3	47.4	71.8	41.7
Extra Help Needed Because of Health										
A lot of extra help (%)	3.7	10.8	5.1	10.9	2.6	5.3	2.9	0.0	2.6	8.3
Some extra help (%)	18.1	33.8	13.0	27.3	15.8	26.3	17.1	31.6	17.9	50.0
A little extra help (%)	31.4	30.8	20.9	30.9	24.6	36.8	12.9	26.3	15.4	8.3
No more help than a healthy person (%)	46.8	24.6	61.0	30.9	57.0	31.6	67.1	42.1	64.1	33.3

appearance as a result of their transplant experience. A summary of transplant patients' feelings about their appearance 3, 6, 9, 12, and 15 months following transplant surgery by initial immunosuppressive protocol and by primary renal diagnosis are shown in Tables 11-14 and 11-15, respectively. In general, patients are more likely to think that their transplant affects their appearance, and are less likely to be happy about their appearance as time since transplantation increases. Over time, patients are more likely to feel that they are too fat, and therefore less likely to feel that they are too thin or just right than they were three months following their surgery. While 21.3 percent of patients said that they are very happy with their appearance three months posttransplant, only 13.5 percent of patients said that they are very happy about their appearance 15 months posttransplant. Again, although feelings about their appearance appear to change for patients regardless of their initial immunosuppressive protocol or primary renal diagnosis, diabetic patients continue to be more satisfied with their appearance than nondiabetic patients.

Personal Adjustment to the Transplant--

As noted earlier, three months following transplant surgery, the vast majority of patients (71.1%) feel that they have adjusted very well to their transplant and most (75.6%) said that they are generally happier than they were before they had their transplants. As can be seen in Tables 11-16 and 11-17, as time since transplantation increases, the percentage of patients who feel that they have adjusted very well increases. By 15 months posttransplant, 78.8 percent of all patients say that they have adjusted very

Table 11-14
Feelings About Appearance of Participating Transplant Recipients 3, 6, 9, 12, and 15 Months Following Transplant Surgery by Initial Immunosuppressive Protocol

	3 Months Posttransplant		6 Months Posttransplant		9 Months Posttransplant		12 Months Posttransplant		15 Months Posttransplant	
	AZA+PRED+ALG	CSA+PRED	AZA+PRED+ALG	CSA+PRED	AZA+PRED+ALG	CSA+PRED	AZA+PRED+ALG	CSA+PRED	AZA+PRED+ALG	CSA+PRED
Does Transplant Affect Appearance										
Yes (%)	66.7	61.4	64.4	65.2	60.0	59.6	60.8	60.5	72.7	42.1
No (%)	33.3	38.6	35.6	34.8	40.0	40.4	39.2	39.5	27.3	57.9
Do You Think You Are:										
Too fat (%)	49.7	42.2	52.5	47.8	60.0	57.9	58.8	50.0	72.7	52.6
Just right (%)	43.3	42.2	42.6	47.8	36.8	36.8	33.3	42.1	27.3	36.8
Too thin (%)	7.0	15.7	4.9	4.3	3.2	5.3	7.8	7.9	0.0	10.5
Feeling About Appearance:										
Very happy (%)	19.4	25.6	17.3	20.3	12.6	12.3	15.7	21.1	12.1	15.8
Pretty happy (%)	57.1	53.7	53.7	66.7	60.0	64.9	56.9	60.5	57.6	63.2
Not very happy (%)	16.5	14.6	20.4	11.6	16.8	21.1	21.6	15.8	18.2	21.1
Not at all happy (%)	7.1	6.1	8.6	1.4	10.5	1.8	5.9	2.6	12.1	0.0

Table 11-15
Feelings About Appearance of Participating Transplant Recipients 3, 6, 9, 12, and 15 Months Following Transplant Surgery by Primary Renal Diagnosis

	3 Months Posttransplant		6 Months Posttransplant		9 Months Posttransplant		12 Months Posttransplant		15 Months Post Transplant	
	Nondiabetes	Diabetes	Nondiabetes	Diabetes	Nondiabetes	Diabetes	Nondiabetes	Diabetes	Nondiabetes	Diabetes
Does Transplant Affect Appearance										
Yes (%)	64.0	67.7	66.1	60.0	63.2	50.0	60.0	63.2	67.5	41.7
No (%)	36.0	32.3	33.9	40.0	36.8	50.0	40.0	36.8	32.5	58.3
Do You Think You Are:										
Too fat (%)	50.8	36.9	55.7	36.4	63.2	47.4	58.6	42.1	70.0	50.0
Just right (%)	40.2	50.8	39.8	58.2	33.3	47.4	35.7	42.1	27.5	41.7
Too thin (%)	9.0	12.3	4.5	5.5	3.5	5.3	5.7	15.8	2.5	8.3
Feeling About Appearance:										
Very happy (%)	22.3	18.5	16.4	24.1	9.6	21.1	18.6	15.8	15.0	8.3
Pretty happy (%)	55.3	56.9	58.8	53.7	63.2	57.9	57.1	63.2	55.0	75.0
Not very happy (%)	17.0	12.3	18.6	14.8	19.3	15.8	20.0	15.8	20.0	16.7
Not at all happy (%)	5.3	10.8	6.2	7.4	7.9	5.3	4.3	5.3	10.0	0.0

Table 11-16

Personal Adjustment of Participating Transplant Recipients 3, 6, 9, 12, and 15 Months Following Transplant Surgery by Initial Immunosuppressive Protocol

	3 Months Posttransplant		6 Months Posttransplant		9 Months Posttransplant		12 Months Posttransplant		15 Months Posttransplant	
	AZA+PRED+ALG	CSA+PRED	AZA+PRED+ALG	CSA+PRED	AZA+PRED+ALG	CSA+PRED	AZA+PRED+ALG	CSA+PRED	AZA+PRED+ALG	CSA+PRED
How Well Adjusted to Transplant										
Very well (%)	70.6	72.3	72.4	68.1	71.6	78.9	74.5	89.5	78.8	78.9
Fairly well (%)	28.8	26.5	24.5	30.4	25.3	21.1	21.6	10.5	15.2	21.1
Not too well (%)	0.6	1.2	1.8	0.0	1.1	0.0	2.0	0.0	3.0	0.0
Fairly poorly (%)	0.0	0.0	0.6	1.4	0.0	0.0	0.0	0.0	0.0	0.0
Very poorly (%)	0.0	0.0	0.6	0.0	2.1	0.0	2.0	0.0	3.0	0.0
Time Since Transplant Has Been										
About what expected (%)	44.7	38.6	42.9	44.9	41.1	21.1	33.3	18.4	43.8	36.8
Worse than expected (%)	11.2	19.3	8.0	13.0	11.6	7.0	15.7	2.6	9.4	0.0
Better than expected (%)	44.1	42.2	49.1	42.0	47.6	71.9	51.0	78.9	46.9	63.2
How Often Felt Transplant a Mistake										
Never (%)	78.8	73.5	81.0	81.2	87.4	80.7	78.4	92.1	81.8	100.0
Almost never (%)	11.8	12.0	10.4	10.1	8.4	10.5	9.8	7.9	9.1	0.0
Sometimes (%)	6.5	13.3	6.7	4.3	2.1	8.8	7.8	0.0	6.1	0.0
Very often (%)	1.8	1.2	1.8	4.3	1.1	0.0	3.9	0.0	3.0	0.0
Always (%)	1.2	0.0	0.0	0.0	1.1	0.0	0.0	0.0	0.0	0.0
Happiness Compared With Before Transplant										
Happier than before transplant (%)	80.1	66.3	79.1	76.8	71.6	75.4	76.5	86.8	71.9	84.2
Less happy than before transplant (%)	2.9	2.4	6.1	8.7	5.3	0.0	7.8	0.0	12.5	0.0
About as happy as before (%)	15.8	28.9	11.7	11.6	20.0	22.8	7.8	7.9	12.5	10.5
Can't remember (%)	1.2	2.4	3.1	2.9	3.2	1.8	7.8	5.3	3.1	5.3

Table 11-17
Personal Adjustment of Participating Transplant Recipients 3, 6, 9, 12, and 15 Months Following Transplant Surgery by Primary Renal Diagnosis

	3 Months Posttransplant		6 Months Posttransplant		9 Months Posttransplant		12 Months Posttransplant		15 Months Post Transplant	
	Nondiabetes	Diabetes	Nondiabetes	Diabetes	Nondiabetes	Diabetes	Nondiabetes	Diabetes	Nondiabetes	Diabetes
How Well Adjusted to Transplant										
Very well (%)	70.7	72.3	70.6	72.7	75.4	71.1	80.0	84.2	80.0	75.0
Fairly well (%)	28.2	27.7	27.1	23.6	21.9	28.9	17.1	15.8	15.0	25.0
Not too well (%)	1.1	0.0	1.1	1.8	0.9	0.0	1.4	0.0	2.5	0.0
Fairly poorly (%)	0.0	0.0	0.6	1.8	0.0	0.0	0.0	0.0	0.0	0.0
Very poorly (%)	0.0	0.0	0.6	0.0	1.8	0.0	1.4	0.0	2.5	0.0
Time Since Transplant Has Been										
About what expected (%)	45.2	35.4	44.1	41.8	32.5	36.8	30.0	15.8	43.6	33.3
Worse than expected (%)	13.3	15.4	9.6	9.1	9.6	10.5	11.4	5.3	7.7	0.0
Better than expected (%)	41.5	49.2	46.3	49.1	57.9	52.6	58.6	78.9	48.7	66.7
How Often Felt Transplant a Mistake										
Never (%)	75.0	83.1	80.8	81.8	87.7	76.3	84.3	84.2	85.0	100.0
Almost never (%)	13.3	7.7	10.2	10.9	7.0	15.8	8.6	10.5	7.5	0.0
Sometimes (%)	8.5	9.2	6.2	5.5	3.5	7.9	4.3	5.3	5.0	0.0
Very often (%)	2.1	0.0	2.8	1.8	0.9	0.0	2.9	0.0	2.5	0.0
Always (%)	1.1	0.0	0.0	0.0	0.9	0.0	0.0	0.0	0.0	0.0
Happiness Compared With Before Transplant										
Happier than before transplant (%)	76.2	73.8	74.6	90.9	72.8	73.7	78.6	89.5	74.4	83.3
Less happy than before transplant (%)	2.6	3.1	7.3	5.5	3.5	2.6	5.7	0.0	10.3	0.0
About as happy as before (%)	19.0	23.1	14.7	1.8	21.1	21.1	8.6	5.3	12.8	8.3
Can't remember (%)	2.1	0.0	3.4	1.8	2.6	2.6	7.1	5.3	2.6	8.3

well to their transplant and 17.3 percent say that they have adjusted fairly well. Only two of the 52 patients who completed the 15-month follow-up survey provided another response. While even at three months posttransplant the vast majority of all transplant recipients say that they are happier than before they received their transplant, the percentage of patients who report that they are happier than they were before they received their transplant increases over time. This is particularly true among diabetic patients.

Also, with the passage of time, patients are more likely to say that the time since the transplant has been better than expected and fewer patients say that the time has been worse than expected. Similarly, over time patients are less likely to report that they have often felt that their transplant was a mistake. For example, three months following transplant surgery, 77.1 percent of all patients who completed the patient questionnaire reported that they never felt that their transplant was a mistake compared with 88.5 percent of those who completed 15-month follow-up questionnaires. As the time since transplant increases, diabetic patients continue to be more likely than nondiabetic patients to say that the time since the transplant has been better than they expected, as well as more likely to say that they have never felt that their transplant was a mistake. No differences in patients' personal adjustment to the transplant are apparent based on initial immunosuppressive protocol.

Comparisons with Other ESRD Patients and with the General Population

In this section we compare the subjective quality of life of participating renal transplant recipients with data from previous studies of end-stage renal disease (ESRD) patients. In particular, we compare the subjective quality of life of patients in the current study with the subjective quality of life of patients from the National Kidney Dialysis and Kidney Transplantation Study (NKDKTS) (see Evans et al., 1985:553; Evans et al., 1987). These data were collected from a sample of 859 end-stage renal disease patients associated with 11 dialysis and transplant centers throughout the United States. Of the 859 patients included in the study, 287 were treated with home hemodialysis, 347 with in-center hemodialysis, 81 with continuous peritoneal dialysis (CPD), and 144 with transplantation. Of the 144 transplant patients, 74 had received a transplant from a living related donor, and 70 from a cadaver.

Many of the subjective quality of life variables used in our current study were also used in the NKDKTS. Not all variables examined in this chapter were included in the NKDKTS (for example, NKDKTS patients were not asked questions concerning their feelings about their physical appearance). However, we are able to compare patients in terms of a large number of the subjective quality of life indicators examined in this chapter. These include: (1) life satisfaction, happiness and patient well-being; (2) feelings of dependence on others; and (3) personal adjustment to the transplant. Use of standardized measures of life quality also allows us, in certain instances, to compare participating transplant recipients with the general population.

Life Satisfaction, Happiness and Patient Well-Being--

A comparison is made in Table 11-18 of participating renal transplant recipients with ESRD patients from the National Kidney Dialysis and Kidney Transplantation Study in terms of the 15 subjective indicators of life quality.

Table 11-18
Subjective Quality of Life Indicators of Participating Renal Transplant Recipients Compared with National Kidney Dialysis and Kidney Transplantation Study Patients and the General Population

	Transplant Patients*			National Kidney Dialysis and Kidney Transplantation Study					
	All Patients	Nondiabetes	Diabetes	Home Hemodialysis	In-Center Hemodialysis	Continuous Peritoneal Dialysis	Transplant	All Modalities	General Population
Index of Psychological Affect	5.34	5.50	4.86	5.42	5.15	5.24	5.62	5.33	5.68
Index of Well-Being	10.95	11.23	10.17	11.12	10.77	11.05	11.83	11.09	11.77
Overall Life Satisfaction	5.08	5.17	4.82	5.19	5.11	5.30	5.66	5.25	5.55
General Well-Being	4.70	4.72	4.64	4.87	4.79	4.74	4.81	4.82	---
Positive Affect Scale	3.47	3.50	3.38	3.21	2.62	2.90	3.60	3.01	3.10
Negative Affect Scale	1.73	1.60	2.09	1.70	1.82	1.86	1.93	1.80	1.60
Affect Balance Scale	5.75	5.95	5.32	5.59	4.95	5.22	5.81	5.34	5.60
General Life Satisfaction	1.70	1.74	1.57	1.69	1.67	1.67	1.73	1.69	---
Satisfaction With Marriage	5.73	5.77	5.60	6.44	5.96	6.33	6.20	6.23	6.27
Satisfaction With Family Life	5.41	5.54	5.03	5.82	5.54	6.04	5.62	5.69	5.92
Satisfaction With Friendships	5.36	5.43	5.17	5.54	5.29	5.47	5.43	5.41	5.74
Satisfaction With Savings and Investments	4.11	4.17	3.94	4.57	4.45	4.81	4.35	4.51	4.27
Satisfaction With Standard of Living	5.01	5.02	4.98	5.59	5.22	5.70	5.49	5.44	5.31
Feeling About Present Life (hard, easy)	4.66	4.75	4.39	4.50	4.40	4.55	4.64	4.49	4.43
Feeling About Present Life (tied down, free)	4.86	5.07	4.25	4.01	4.34	4.50	5.41	4.43	5.31

*Subjective Quality of Life for participating transplant recipients as measured 3 months posttransplant.

The quality of life indicators shown for participating transplant recipients were measured three months following surgery. Values of the quality of life indicators are shown separately by primary renal diagnosis (nondiabetes versus diabetes). The table also compares the quality of life of NKDKTS patients (overall and by treatment modality) and the general population as measured by 13 of the 15 quality of life indicators.

The results of the National Kidney Dialysis and Kidney Transplantation Study (Evans et al., 1987) concluded that, in general, transplant patients report higher quality of life according to most subjective indicators of life quality than patients on the other ESRD treatment modalities. In addition, when compared with the general population, patients with end-stage renal disease rate their quality of life similarly. As shown in Table 11-18, comparing the subjective quality of life of participating transplant recipients three months following surgery with National Kidney Dialysis and Kidney Transplantation Study patients, transplant recipients from this study generally report lower quality of life than NKDKTS transplant patients. Likewise, the quality of life of the transplant patients included in the current study appears to be lower than that of the general population.

A comparison of the quality of life of diabetic and nondiabetic patients from the current study with the quality of life of patients from the NKDKTS is also shown in Table 11-18. Clearly, the quality of life of nondiabetic transplant patients in the current study more closely resembles the quality of life reported by transplant patients from the NKDKTS. Diabetic transplant patients, on the other hand, more closely resemble NKDKTS in-center hemodialysis patients in terms of their subjective quality of life. In the case of several of the subjective quality of life measures, these diabetic transplant patients report a somewhat lower quality of life than the in-center hemodialysis patients.

The lower subjective life quality reported in this study compared with transplant patients in the NKDKTS is not surprising, however, given differences in the characteristics of the patients included in the two studies. One major difference between the transplant patients from the two studies is in the length of time between transplantation and when patient quality of life was measured. The quality of life data shown in Table 11-18 are for transplant patients three months following surgery, whereas the quality of life of transplant patients in the NKDKTS was measured an average of 4.28 years following transplantation. Indeed, only 19.4 percent of transplant patients in the NKDKTS sample had received their transplants less than one year prior to data collection. In addition, the average age of the transplant patients in the NKDKTS was 37.2 years compared to 42.2 years for patients in the current study. Finally, 26.5 percent of all patients included in the current study are diabetic patients, compared with only 7.9 percent of transplant patients from the National Kidney Dialysis and Kidney Transplantation Study. Thus, differences in the composition of the transplant patients included in the two studies (e.g., length of time since transplantation, proportion of diabetic patients) may account for the subjective quality of life differences seen in Table 11-18.

As is shown in Table 11-19, when compared with patients from the National Kidney Dialysis and Kidney Transplantation Study, three months after surgery transplant patients in the current study express lower levels of general happiness. Transplant patients in the current study are less likely to say that they are very happy and more likely to say that they are not too

Table 11.19
Levels of Happiness Expressed by Participating Transplant Recipients Compared With National Kidney Dialysis and Kidney Transplantation Study Patients

	Transplant Patients*			National Kidney Dialysis and Kidney Transplantation Study				
	All Patients	Nondiabetes	Diabetes	Home Hemodialysis	In-Center Hemodialysis	Continuous Peritoneal Dialysis	Transplant	All Modalities
Level of Happiness								
Very Happy (%)	25.8	28.9	16.9	30.9	23.5	23.5	48.2	30.1
Pretty Happy (%)	64.7	63.6	67.7	58.2	61.0	64.2	46.8	58.0
Not too Happy (%)	9.5	7.5	15.4	10.9	15.5	12.3	5.0	11.9
Enjoyment of Life Compared With Others								
More than Others (%)	34.2	36.5	27.5	45.7	38.8	40.0	41.3	41.7
About the Same (%)	56.5	56.5	56.5	44.0	51.2	48.7	52.4	48.7
Less than Others (%)	9.3	7.0	15.9	10.3	10.0	11.2	6.3	9.6
Quality of Life Compared With Others (%)								
Better (%)	26.2	27.3	24.6	25.2	18.6	21.0	25.4	22.2
About the Same (%)	58.7	61.0	52.3	58.2	65.0	66.7	65.5	62.9
Lower (%)	14.7	11.8	23.1	16.7	16.5	12.3	9.2	14.9

*Levels of Happiness expressed by participating transplant recipients as measured three months posttransplant.

happy, than transplant patients in the NKDKTS. Similarly, NKDKTS transplant patients are more likely to say that they have enjoyed life more than others they know and less likely to say that their quality of life is lower than others they know. By 15 months posttransplant (Table 11-11), nondiabetic patients in the current study rather closely resemble the transplant patients in the NKDKTS with respect to their general level of happiness. Diabetic patients, on the other hand, more closely resemble the NKDKTS in-center dialysis patients.

A comparison of the levels of happiness of participating transplant recipients at 3 and 15 months posttransplant with the general population (Campbell et al., 1976:26) is presented in Table 11-20. When asked about their general level of happiness three months following surgery, the responses of participating kidney transplant patients are almost identical to the responses of the general population for the most recent years reported in the table. When asked about their general level of happiness 15 months following surgery, transplant patients in the current study generally report higher levels of happiness than the general population. However, as noted earlier, reported levels of happiness differ greatly by primary renal diagnosis. A much higher percentage of nondiabetic patients say that they are very happy than is true for the general population. In contrast, a higher percentage of diabetic patients report that they are not too happy compared with the general population.

Feelings of Dependence on Others--

Table 11-21 compares the responses of participating transplant recipients and end-stage renal disease patients from the National Kidney

Table 11-20
Level of Happiness Expressed by Participating Transplant Recipients Compared with the General Population (Expressed as a Percentage)

	Very Happy	Pretty Happy	Not Too Happy
Transplant Patients (3 Month Follow-up)			
All patients	25.8	64.7	9.5
Nondiabetic patients	28.9	63.6	7.5
Diabetic patients	16.9	67.7	15.4
Transplant Patients (15 Month Follow-up)			
All patients	38.5	51.9	9.6
Nondiabetic patients	42.5	50.0	7.5
Diabetic patients	25.0	58.3	16.7
General Population - 1957	35	54	11
General Population - 1963	32	52	16
General Population - 1965	30	53	17
General Population - 1971	29	61	10
General Population - 1972	26	65	9
General Population - 1972	22	68	10

Table 11-21
Problems of Dependence on Others of Participating Transplant Recipients Compared With National Kidney Dialysis and Kidney Transplantation Study Patients

	Transplant Patients*		National Kidney Dialysis and Kidney Transplantation Study				
	Nondiabetes	Diabetes	Home Hemodialysis	In-Center Hemodialysis	Continuous Peritoneal Dialysis	Transplant	All Modalities
Degree of Independence							
Very independent (%)	45.7	24.6	34.7	42.9	27.2	44.4	38.9
Pretty independent (%)	47.3	50.8	56.5	43.5	58.0	49.3	50.2
Not very independent (%)	3.4	21.5	7.0	9.6	9.9	4.9	8.0
Not at all independent (%)	3.7	3.1	1.8	4.1	4.9	1.4	2.9
Feelings About Dependence							
Are more dependent than would like to be (%)	29.9	56.9	59.6	45.8	58.7	30.6	49.0
Would like to have someone to depend on more (%)	6.4	7.7	4.6	9.9	2.5	5.6	6.7
Neither (%)	63.6	35.4	35.8	44.3	38.7	63.9	44.3

*Problems of Dependence on Others of participating transplant recipients as measured three months posttransplant.

Dialysis and Kidney Transplantation Study to questions concerning their feelings of dependence on others. Responses to these questions are consistent with responses to the subjective quality of life measures discussed previously. Nondiabetic patients in the current renal transplantation study, like transplant patients in the NKDKTS, are equally likely to feel that they are very independent or pretty independent in managing their own lives. Diabetic patients, on the other hand, report that they are even less independent in managing their own lives than dialysis patients from the NKDKTS. Indeed, these diabetic patients most closely resemble NKDKTS continuous peritoneal dialysis patients in their responses.

Similarly, the percentage of nondiabetic patients who said that they are more dependent on others than they would like to be was similar to transplant patients from the NKDKTS. The responses of diabetic patients to this same question was much higher, similar to home hemodialysis and continuous peritoneal dialysis patients from the NKDKTS.

Personal Adjustment to the Transplant--

Following their transplant surgery, participating transplant recipients were asked how well they think they have adjusted to their transplants. Patients in the National Kidney Dialysis and Kidney Transplantation Study were asked how well they think they have adjusted to their dialysis treatments or to their kidney transplant. Table 11-22 compares the responses of transplant patients from the current study and dialysis and transplant patients from the NKDKTS. The responses of transplant patients in the current study were similar to the responses of NKDKTS transplant patients regarding their personal adjustment to their transplant. As noted

Table 11-22
Personal Adjustment of Participating Transplant Recipients Compared With National Kidney Dialysis and Kidney Transplantation Study Patients

	Transplant Patients		National Kidney Dialysis and Kidney Transplantation Study				
	3 Months Posttransplant	15 Months Posttransplant	Home Hemodialysis	In-Center Hemodialysis	Continuous Peritoneal Dialysis	Transplant	All Modalities
How Well Adjusted to transplant							
Very well (%)	71.7	78.8	69.0	57.8	67.9	82.6	66.7
Fairly well (%)	28.1	17.3	27.5	35.8	30.9	15.3	29.1
Not too well (%)	0.8	1.9	1.4	4.9	0.0	2.1	2.8
Fairly poorly (%)	0.0	0.0	0.7	0.6	1.2	0.0	0.6
Very poorly (%)	0.0	1.9	1.4	0.9	0.0	0.0	0.8

earlier, with the passage of time, transplant patients were more likely to say that they had adjusted very well to their transplant. Fifteen months following surgery 78.8 percent of transplant recipients from the current study said that they had adjusted very well, compared with 82.6 percent of NKDKTS transplant patients (who, on average, were interviewed four years after transplantation).

Discussion

In previous chapters of this report we examined the quality of life of renal transplant recipients following surgery using various objective indicators of life quality (e.g., employment status, functional impairment, health status). In this chapter we focused our analysis on the quality of life of renal transplant recipients using several subjective measures. These included a variety of indices of general life satisfaction and patient well-being, as well as several measures focusing on more narrowly-defined aspects of one's life experience. Quality of life was examined at several points in time--at 3-months, 6-months, 9-months, 12-months, and 15-months posttransplant. Similar to the approach used in previous chapters, differences in the various subjective quality of life indicators were examined separately for patients in the two initial immunosuppressive protocol groups (AZA + PRED + ALG versus CSA + PRED), and for patients grouped by primary renal diagnosis (diabetes versus nondiabetes).

Despite certain limitations in physical functioning and reduced labor force participation, transplant recipients are generally quite satisfied with their lives following their transplant surgery. Overall, patients feel that they have adjusted well to their transplants. The vast majority of kidney transplant recipients report that they are happier following transplantation than they were prior to their transplant. In general transplant patients feel that they are either very independent or pretty independent in managing their lives. Thus, dependence on others is not viewed as a major problem among most renal transplant recipients. Indeed, patients generally feel that the time since their transplant has either been about what they expected or better than they expected. The overwhelming majority of transplant recipients have never felt that their transplant was a mistake.

In our previous analyses we found that in terms of employment status, functional impairment, and health status, the quality of life of renal transplant patients improves over time in the months following transplant surgery. However, the improvement in these outcome variables is not reflected in reported levels of life satisfaction, happiness, and general well-being. Indeed, there is surprisingly little variation in the subjective quality of life measures over time. These findings are consistent with our previous research suggesting that, although they are positively correlated, the level of correlation between various objective and subjective indicators of life quality is not high (Evans et al., 1985:553; 1987).

Initial immunosuppressive protocol does not influence renal transplant patients' subjective quality of life in the months following transplant surgery. However, the subjective quality of life of patients does differ by primary renal diagnosis. In our previous analyses we concluded that diabetic patients have a lower quality of life than nondiabetic patients in terms of various objective indicators of life quality. For example, we found that diabetic patients are less likely to be employed, more likely to be functionally impaired, and have lower health status than nondiabetic patients. Perhaps not surprisingly, diabetic patients also report a lower subjective quality of life.

In general, diabetic patients are less satisfied with the quality of their lives and are more likely to feel tied down than are nondiabetic patients. Similarly, they are more likely than nondiabetic patients to say that they have enjoyed life less than others they know and to feel that their quality of life is lower than others they know. Also, dependence upon others is viewed as a somewhat greater problem among diabetic transplant patients than among nondiabetic patients. Diabetic patients regard themselves as considerably less independent than nondiabetic patients in managing their lives.

When asked about their general level of happiness three months following transplant surgery, patients in the current study generally report a level of happiness similar to the general population. By 15 months posttransplant, patients in the current study report higher levels of happiness than the general population. However, reported levels of happiness differ greatly by primary renal diagnosis. A much higher percentage of nondiabetic patients say that they are very happy than is true for the general population. In contrast, a higher percentage of diabetic patients report that they are not too happy compared with the general population.

Finally, quality of life comparisons with end-stage renal disease patients from the National Kidney Dialysis and Kidney Transplantation Study revealed that transplant patients from the current study generally report lower quality of life than transplant patients from the NKDKTS. However, the observed differences in the subjective quality of life indicators can, at least in part, be explained by the characteristics of the transplant patients included in the two studies. Nondiabetic transplant patients in the current study closely resemble the transplant patients from the NKDKTS in terms of subjective quality of life. On the other hand, diabetic transplant patients in the current study more closely resemble NKDKTS in-center hemodialysis patients in terms of their subjective quality of life.

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